Community reinforcement approach and naltrexone in the treatment of addiction

Roozen, H.G.

2005

COMMUNITY REINFORCEMENT APPROACH AND NALTREXONE IN THE TREATMENT OF ADDICTION

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Part of this dissertation was sponsored by The Ministry of Health, Welfare and Sports (VWS) and ZonMw (under grants 3100.0019), Novadic-Kentron, Lamepro, Zambon, STIVORO, and Novartis. Novadic-Kentron and Lamepro supported the publication of this thesis. These agencies had no role in the conduct, interpretation, or analysis of the study.

The research reported in this thesis was conducted in the Research Institute for Psychology & Health, accredited by the Royal Netherlands Academy of Arts and Sciences, at the department of Clinical Psychology of the Vrije Universiteit, Amsterdam, and at Novadic-Kentron, Roosendaal.

vrije Universiteit amsterdam

The Cover: Michelangelo di Lodovico Buonarotti Simoni, the hands of God and Adam (1508-1512), fresco detail from The Sistine Chapel ceiling, Vatican City, Rome.

ISBN-10:	90-9020096-7
ISBN-13:	978-90-9020096-5
Printed by	FEBO druk, Enschede
Lay-out	Onno van Beek & Hendrik Roozen
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VRIJE UNIVERSITEIT

COMMUNITY REINFORCEMENT APPROACH AND NALTREXONE IN THE TREATMENT OF ADDICTION

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. T. Sminia,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de faculteit der Psychologie en Pedagogiek
op dinsdag 29 november 2005 om 15.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

Hendrik Gerrit Roozen

geboren te Doetinchem

promotoren:	prof.dr. A.J.F.M. Kerkhof
	prof.dr. W. van den Brink
copromotoren:	prof.dr. C.A.J. de Jong
	prof.dr. G.M. Schippers

This dissertation contains the following publications or submissions:

Roozen, H.G., Schippers, G.M., Boulogne, J.J., De Jong, C.A.J., Van den Brink, W., & Kerkhof, A.J.F.M. CRA in treating addiction: a conceptual/historical analysis. *Submitted.*

Roozen, H.G., Boulogne, J.J., Van Tulder, M.W., Van den Brink, W., De Jong, C.A.J., & Kerkhof, A.J.F.M. (2004). A systematic review of the effectiveness of the CRA in alcohol, cocaine and opioid addiction, *Drug and Alcohol Dependence*, **74**, 1-13.

Roozen, H.G., De Waart, R, Van der Windt, D.A.W.N., Van den Brink, W., De Jong, C.A.J., & Kerkhof, A.J.F.M. A systematic review of the effectiveness of naltrexone in the treatment of opioid and alcohol dependence. *Submitted.*

Roozen, H.G., Kerkhof, A.J.F.M., & Van den Brink, W. (2003). Experiences with an outpatient relapse program (CRA) combined with Naltrexone in the treatment of opioid-dependence: effect on addictive behaviors and the predictive value of psychiatric comorbidity, *European Addiction Research*, **9**, 53-58.

De Jong, C.A.J., Roozen, H.G., Krabbe, P.F.M., Van Rossum, L., & Kerkhof A.J.F.M. High abstinence rates in heroin addicts by a new comprehensive treatment approach. *Submitted.*

Roozen, H.G., van Beers, S.E.C., Weevers, H.J.A., Breteler, M.H.M., Willemsen, M.C., Postmus, P.E., & Kerkhof, A.J.F.M. Effects on smoking cessation: naltrexone combined with a cognitive behavioral treatment based on the Community Reinforcement Approach. *Accepted in Substance Use & Misuse.*

Contents

CHAPTER 1

General Introduction

General introduction

Addiction is considered a chronic relapsing disorder with biological, psychological and social causes and consequences (McLellan, 2002). The DSM (American Psychiatric Association, 1995, p. 9-10) and the ICD (World Health Organization, 1992) define substance use disorders as a substance dependence syndrome and/or substance abuse (DSM) or harmful use (ICD). Substance use disorders are characterized by a cluster of physiological, behavioral, and cognitive phenomena in which the use of a substance takes on a much higher priority for a given individual than other behaviors that once had greater value. A central descriptive characteristic is the desire (often strong, sometimes overpowering) to take the substance (which may, or may not, have been medically prescribed).

Treatment goals range from cure through care to palliation (Van den Brink & Van Ree, 2003). Even though addiction is considered to be a chronic relapsing disease, the ambition of many patients, therapists and policy makers is still the cure of this disease, i.e. stable abstinence. This dissertation focuses on this goal. In order to obtain this goal, it is believed that pharmacological interventions should be integrated with psychosocial treatments to obtain optimal results (Kleber et al., 2003). For instance, it is said that naltrexone-assisted detoxification followed by naltrexone maintenance treatment should be integrated with psychosocial support measures, such as CRA (De Jong et al, 2004; Roozen et al., 2000). Obviously, such an integrated treatment approach should be systematically evaluated before it can be implemented in general practice. The introduction ends with the research questions for this evaluation and a brief outline of the content of this thesis.

1.1. Substance use disorder: a chronic relapsing disorder

1.1.1. Prevalence of substance use

Recent data from the United Nations suggests that worldwide about 180 million people - 4.2 per cent of people aged 15 years and above - were consuming illicit drugs in the late 1990s (United Nations Office for Drug Control and Crime Prevention, 2001). This estimated number includes 9 million heroin users, 29 million people consuming amphetamine-type stimulants, and 14 million people using cocaine. In addition, there are worldwide about 1.2 billion smokers of tobacco products (World Health Organisation, 2004).

Twelve percent of the US population reported using cocaine one or more times in their lifetime (American Psychiatric Association, 1995). It is estimated that there are currently one million cocaine dependent persons in the US (Substance Abuse and Mental Health Services Administration, 1999). In Western Europe there are some 1.2 million-heroin dependent persons and the US estimates that there are approximately 1 million heroin dependent persons (United Nations Office for Drug Control and Crime Prevention, 2001, p.4; Substance Abuse and Mental Health Services Administration, 1999). In the US there are about 3.1 million people using marijuana on a daily or almost daily basis over a 12-month period (National Survey on Drug Use and Health, 2002; National Institute on Drug Abuse, 2004). An estimated 15 million Americans are dependent on alcohol (National Institute on Alcohol Abuse and Alcoholism, 2004), which indicates that about 14% of American adults had either alcohol dependence or abuse sometime in their lives (Helzer, Burnam, & McEvoy, 1991). Although there are no exact data available, Europe is the region of the world with the highest production and consumption of alcohol and 5% of European adults are currently dependent on alcohol (Eurocare, 2004).

In the Netherlands, with a population of about 16 million inhabitants, there are approximately 26,000-30,000 heroin dependent persons and 820,000 alcohol-abusing people (Netherlands National Drug Monitor, 2003). About 366,000 of these problematic alcohol users are dependent (Bijl, Van Zessen, & Ravelli, 1997). Furthermore, in the Netherlands it is estimated that there are approximately four million smokers (Netherlands National Drug Monitor, 2003)

and an estimated 2.4 million are dependent on nicotine (Netherlands National Drug Monitor, 2001; Health Counsel of the Netherlands, 2002a, p. 63). Recently, the percentage of heavily smoking people has fallen (Netherlands National Drug Monitor, 2003; Koolhaas, 2004). The percentage of cannabis users is currently about 3% (408,000; Netherlands National Drug Monitor, 2003). Cannabis is the most popular of all illicit drugs (Netherlands National Drug Monitor, 2003). In the general population, the percentage of present cocaine users is 0.4% and 0.5% for amphetamine users (Netherlands National Drug Monitor, 2003). Unfortunately, no exact numbers of cocaine and amphetamine dependent persons are available for the Netherlands (Health Counsel of the Netherlands, 2002a).

1.1.2. Consequences of substance use disorders

Substance use disorders are associated with medical, economic, psychiatric, family, and legal problems (McLellan et al., 1994). It affects health by accompanying coexisting medical illness of drug users (Kresina et al., 2004; Stein, 1990), which is often related to the route of drug administration. Many substance users seem to have severe problems with infectious diseases (De la Fuente et al., 1996; Kresina et al., 2004) such as bacterial endocarditis, osteomyelitis, septic arthritis, and most commonly, skin infections such as abscesses and cellulitis (Stein, 1990; Leri, Bruneau, & Stewart, 2003). Above all, injection drug use is a profound risk factor for the transmission of HIV infection (US Centres for Disease Control and Prevention, 1993; Jurgens, 2003), Hepatitis A, B, C and D, and other retroviral infections (O'Connor & Selwyn, 1997; Macalino et al., 2004; Vlahov et al., 2004). Due to environmental and social factors related to substance dependence, diseases such as pneumonia, tuberculosis and sexually transmitted diseases can impair the health status of drug users.

Along with the medical complications listed above, the use of substances can also have profound direct implications on health. For instance, heroin and other opiates can cause arrhythmias and noncardiac pulmonary edema, and may reduce cardiac output (Frishman et al., 2003). Alcohol can cause a variety of problems such as central nervous system complications (e.g. Korsakov

syndrome), cardiovascular problems (e.g. chronic cardiomyopathy, hypertension, and arrhythmia) (Frishman et al., 2003), and gastrointestinal diseases (e.g. liver cirrhosis, pancreatitis) (O'Connor, 1994). Problematic cocaine use on the other hand is mainly associated with cerebral- or cardio vascular diseases such as cerebral vasculitis, intracranial hemorrhage, cerebral infarction, and stroke (O'Connor et al., 1992; Su et al., 2003). Heavy use of 3,4 methylenedioxy-methamphetamine (MDMA/XTC) is associated with neurotoxic effects on serotonin neurons (Reneman et al., 2001). Smoking is associated with Chronic Obstructive Pulmonary Diseases (COPD) and lung cancer (Health Counsel of the Netherlands, 2002a).

The often co-occurring social impairments and the presence of comorbid psychiatric disorders such as depression, anxiety, and personality disorders are associated with negative treatment outcomes (De Jong et al., 1993; Moos, Finney & Cronkite, 1990). These problems precipitate often in disrupted interpersonal relationships, absenteeism, job loss, criminal behavior, and poor academic or work performance (American Psychiatric Association, 1995, p. 12). Maladaptive coping strategies and limitation of activities, mainly focused on obtaining and using substances are, in general, linked with elevated levels of life threatening behavior. These include criminal behavior, violence, property crimes and other types of crimes, and often lead to imprisonment. It is estimated that about 40% (range 19%-56%) of all prisoners have a substance related disorder (Blaauw, Roesch & Kerkhof, 2000; Koeter & Luhrman, 1998; Health Council of The Netherlands, 2002b). Other life threatening types of behavior may lead to accidents, suicide, violence, AIDS, and cause death among drug users (Hulse et al., 1999; Rossow & Lauritzen, 1999). Consequently, the mortality of substance dependence is high (Hulse et al., 1999). "Economic reliance on the drug trade, and drug addiction, leaves many individuals open to exploitation by criminals and criminal organizations; threatening the health of men, women and children, the rule of law, and ultimately, the vitality and strength of all our communities" (United Nations Office for Drug Control and Crime Prevention, 2001, p. 173).

1.1.3. Substance use disorders have a chronic intermittent course

More than thirty years ago, Hunt, Barnett and Branch (1971) demonstrated the high relapse rates of addiction treatment outcome and found that treatment is associated with high rates of recidivism across a wide range of addictive behaviors. In addition, the data showed that about two-thirds of all participants relapsed within the first 90 days (Marlatt & Gordon, 1985, p. 35). The temporal patterning of relapse in a spectrum of different addictions exhibits a remarkable consistent curve (Marlatt & Gordon, 1985, p. 34). The curve characterizes a cumulative one (percentage of abstainers remaining at interval over a given period) and has a downward slope.

A predominant factor that often results in relapse is treatment dropout or treatment non-compliance (McCusker et al., 1996). In general, dropout in substance abuse treatment is very high (see De Weert-Van Oene, 2000). Dropout in outpatient alcohol and drug programs generally varied, between 44-80%. Dropout in alcohol and drug inpatient programs typically varied, between 18-96% (Stark, 1992).

The recurrences of relapse and dropout have influenced our view of addiction. For many people substance use has become a chronic relapsing disorder, and repeated treatment episodes are required before the individual achieves long-term abstinence (O'Brien & McLellan, 1996; McLellan et al., 2000; McLellan, 2002). The chronic nature of addiction is suggested to be the result of the prolonged effects of drugs on the brain (Leshner, 1997). This chronicity is illustrated in a twenty year follow-up study of heroin dependent patients, published more than thirty years ago, ascertaining that 23% died (mostly of unnatural causes), outcome was uncertain in 10%, about 25% were still known to be using drugs and 35-42% had reached stable abstinence (Vaillant, 1973). More recent, the same author conducted a study to determine the course of male alcohol abusing patients from the age of 40 years to 60 or 70 years. It was found that, by 60 years of age, 18-28% of the patients had died, 11-30% were abstinent, 11% were controlled drinkers, and 28-59% were known to be still abusing alcohol (Vaillant, 1996). In addition, the author stated that a return to controlled drinking without

eventual relapse was unlikely. Alcohol abuse could continue for decades without remission or progression of symptoms (Vaillant, 1996).

More evidence for the chronic nature of opioid dependence is provided by the study of Hser. This study showed that, while the number of deaths increased steadily over time, heroin use patterns were remarkably stable for the group as a whole. Furthermore, the authors stated that for some, heroin addiction has been a lifelong condition associated with severe health and social consequences (Hser et al., 2001). Accordingly, Hser stated: “Abstinence for 5 years significantly reduced the likelihood of relapse, but even among those who achieved 15 years of abstinence, a quarter still relapsed” (cited from Zickler, 2001).

In summary, addiction appears to be a chronic relapsing disorder with a strong biopsychological underpinning and with serious medical, psychological and social consequences. Treatment should take all these aspects into account in order to promote positive outcomes. To address the chronicity, abstinence oriented treatments are viable, as it was shown that cocaine abstinence achieved during treatment was the single best predictor of cocaine abstinence during follow-up (Carroll et al., 1994; Higgins et al., 2000a,b; Kosten et al., 1992). Similar outcomes have been found in studies of individuals attempting to discontinue use of cigarettes, and individuals attempting to lose weight and maintain weight loss, suggesting a common mechanism for treatment success (Higgins et al., 2000b). It may be concluded that recovery oriented treatment approaches, which facilitate short-term abstinence, predict long term-treatment success (Weisner et al., 2003). Additionally, these findings highlight the beneficial impact of readmission and the principles of recycling.

1.2. Treatment goals

In the western world, the disease model (Jellinek, 1960) is prevalent. For most patients with alcohol dependence, abstinence is still the primary and optimal goal (American Psychiatric Association, 1995; Rosenberg & Davis, 1994). However,

there is a wealth of complementary treatment options that emphasize alternative goals, such as controlled drinking or the prevention of medical complications. In the field of opiate management, these treatments are labeled 'harm reduction' and 'risk minimization', and are embodied in programs such as buprenorphine or methadone maintenance treatment. Presently, methadone maintenance is regarded as a cornerstone in the treatment of heroin dependence (Fiellin & O'Connor, 2002). Harm reduction addresses substance dependence from a health perspective and considers any reduction of concomitant negative effects as valuable (Gunn, White & Srinivasan, 1998). "Harm reduction encompasses abstinence as a desirable goal, but recognizes that when abstinence is not possible, it is not ethical to ignore the other available means of reducing human suffering" (Gunn, White & Srinivasan, 1998, p. 1191).

The clients' motivation -especially readiness for treatment- is an important predictor of retention and therapeutic engagement (Joe, Simpson & Broome, 1998). In general, motivational enhancement is considered as an important part of a broader treatment package. Motivational enhancement depicts a set of techniques based on Motivational Interviewing, which can be used to increase patients' motivation to initiate a commitment toward the preferred treatment goal. Motivational Interviewing principles are based on motivational psychology and are designed to produce rapid, internally motivated change (Miller & Rollnick, 1992). "This treatment strategy does not attempt to guide and train the subject, through recovery, but instead employs motivational strategies to mobilize the client's own change resources" (Miller et al., 1992, p. 1).

In Motivational Interviewing, the responsibility for the change in behavior is left to the patient; it is assumed that patients can use available resources to change behavior and that training is not required. By using Motivational Interviewing techniques, the subject moves from the pre-contemplation stage through the contemplation stage to the preparation stage, where plans can be made for behavior change, in accordance with the treatment goal. Accordingly, the Health Counsel of the Netherlands (2002a, p. 73), distinguished three hierarchically ordered goals for the treatment of patients with substance use disorders:

1. ‘Cure’ by the achievement of stable abstinence. In general, ‘curing’ addiction is considered to be possible only when substance-using behavior is fully discontinued. Cure is focused on stable abstinence. This goal can only be reached by the combination of:
   - *detoxification.* The main objective is to relieve withdrawal symptoms, evoked by discontinuation of substance use. Each substance has a specific intrinsic pharmacological profile, which has implications for the severity and duration of withdrawal symptoms and the detoxification process. Withdrawal symptoms can be controlled by means of either inpatient- or outpatient treatment. For instance, alcohol dependent patients may require inpatient detoxification with additional pharmacological attenuation therapy with tranquilizers, in patients with a history of severe or abnormal withdrawal reactions. Related to the chosen detoxification technique, it is important to manage and monitor withdrawal symptoms and detect complications such as delirium tremens, dehydration, and other somatic or psychiatric deterioration. This is especially important for the use of accelerated invasive procedures in which antagonists precipitate acute severe withdrawal symptoms, such as rapid opioid detoxification (Roozen et al., 2002). In general, the detoxification process does not address underlying mechanisms related to initiation and maintenance of addiction, and thus is not an adequate treatment in itself (Mattick & Hall, 1996). It can only be considered as an initial start towards the goal of long-term recovery. Detoxification should be followed by:
   - *relapse prevention*, which implies a focus on the prevention of relapse after abstinence is initiated. Relapse prevention constitutes a collection of interdependent pharmacological and psychosocial techniques designed to foster abstinence. The methods and techniques involved in the current study will be explained in the next paragraphs: psychosocial treatment methods (1.4.1) and pharmacological treatment (1.4.2).

2. When cure (stable abstinence) is not obtainable, care, stabilization or risk minimization, i.e. reduction in frequency and intensity of substance use and

associated sequels, and reduction in the use and effects of substances (American Psychiatric Association, 1995, p. 16) becomes the objective. The subject will be referred to a maintenance program, which is designated to stabilize or regulate the use of illegal substances. Currently, pharmacological maintenance strategies are only available for smoking (nicotine replacement therapy) and opiate dependence (methadone and buprenorphine maintenance). Patients may also benefit from additional psychosocial treatments. These interventions will be outlined in paragraph 1.4.1.

- The aim of Nicotine Replacement Therapy by the available forms (nicotine gum, transdermal patch, the nicotine nasal spray, nicotine inhaler and nicotine sublingual tablets/lozenges) is to replace nicotine from cigarettes to reduce smoking. The commonly used transdermal patches are available in different sizes, and deliver between 7 mg and 22 mg of nicotine over a 24-hour period, resulting in plasma levels similar to the trough levels seen in heavily smoking persons (Fiore, 1994). NRTs are effective as part of a strategy to promote smoking cessation (Silagy et al., 2002, 2004).
- In the case of opiate dependence, methadone and buprenorphine are the most frequently applied substitution compounds. In the treatment of opiate use disorder, the use of methadone, a long acting opioid agonist, is considered as an effective pharmacological maintenance treatment for heroin dependence. It acts by reducing acute subjective effects of heroin and other illicit opiates through the mechanism of cross-tolerance (Litten & Allen, 1999). A meta-analysis demonstrated that methadone is statistically significantly more effective than non-pharmacological approaches in retaining patients in treatment and in the suppression of heroin use, but methadone was not statistically superior in the reduction of criminal activities (Mattick et al., 2002a). Another pharmacological agent is buprenorphine, which differs from methadone in exhibiting reduced (partial) agonist activity with increasing doses (Lewis, 1985). Buprenorphine has a higher affinity for μ-opioid receptor sites than methadone and heroin, and it has been reported to be an alternative to

methadone for maintenance treatment of opioid dependent patients. Buprenorphine reduces heroin use, blocks subjective and physiological effects of other opiates, and augments treatment retention (Litten & Allen, 1999). A recent review has shown that buprenorphine suppressed heroin use significantly better than placebo, but it is not more effective than methadone at adequate dosages (Mattick et al., 2002b). An advantage of buprenorphine over methadone is its low liability of physical dependence and, therefore, it can be withdrawn or tapered with relative ease (Litten et al., 1997). However, there is a worrying increase in the number of reports of illegal intravenous injection of crushed buprenorphine tablets to which deaths were attributed (Kintz, 2002).

3. Palliation is considered as the third goal, aimed to treat symptoms and to reduce suffering associated with chronic addiction in patients with short lifetime expectancy. Palliation focuses on the individual experience of the advanced disease process, not on the disease process itself. The goals of palliation are aimed at reducing suffering, increasing comfort, and quality of life. When cure or risk minimization is no longer obtainable, palliation can be considered as an option for patients who are facing a terminal illness.

1.3. Detoxification strategies

Detoxification can be conducted in both an outpatient or inpatient setting. Inpatient detoxification allows the patient to be closely monitored; a controlled setting may minimize the exposure to the substance of use, and can accelerate the process of detoxification. Outpatient detoxification has the advantage of being less disruptive to the patient's life. The choice of setting depends on factors such as the type of substance, multiple substance use, amount and length of history of dependence (there is a potential for developing dangerous abstinence symptoms including seizure or delirium), psychosocial issues (lack of social support at

home), the patient's age, and co-existing medical and/or psychiatric conditions (psychopathology, suicidal ideations, comorbid medical conditions) and insufficient response to earlier outpatient detoxification.

In general, there are two strategies for the management of withdrawal symptoms: (1) suppression of withdrawal by a cross-tolerant medication (e.g. benzodiazepines, or an opioid agonist such as methadone), and (2) decreasing signs and symptoms of withdrawal by alteration of another neuropharmacological process (e.g. alfa adrenergic agonists such as clonidine or lofexidine). Either one or both strategies together may be used to manage withdrawal syndromes effectively. In order to suppress withdrawal with cross-tolerant medication, a longer-acting medication typically is used to provide a milder, controlled withdrawal and involves dose tapering.

Through the use of opioid antagonists, i.e. naltrexone, with or without general anesthesia, opiate detoxification can be accelerated and completed within 24-72 hours, respectively. A recent review found that it was impossible to draw any conclusions about the long-term effectiveness, or the cost-effectiveness, of withdrawal induced by opioid antagonists under heavy sedation or anesthesia (Gowing et al., 2002a). Although rapid detoxification with the use of opioid-antagonists combined with α-2 (adrenergic) agonists is considered as feasible (Gowing et al., 2002b), the anesthesia-managed approach remains experimental (Gowing et al., 2002a).

1.4. Relapse prevention strategies

In general, treatments aimed at changing addictive behaviors involve both “knowing how”, which is related to self-control and adopting skills, and “wanting to”, which is related to motivation. Changing addictive behaviors is the main treatment goal in both cure and care. To facilitate change, a broad spectrum of psychosocial and pharmacological treatments has been developed. Several psychosocial treatments have been associated with positive treatment outcomes.

In addition, there are also evidence based pharmacological agents available. Because addiction is a condition with a biopsychosocial etiology, pharmacotherapy should be part of an integrated treatment approach, which also addresses psychosocial elements (Health Counsel of the Netherlands, 2002a, p. 27).

Several psychosocial and pharmacological treatments are considered to be effective in the treatment of substance use disorders (e.g. American Psychiatric Association, 1995, p. 2; Carroll, 1998; Miller & Wilbourne, 2002; National Institute on Drug Abuse, 1999; Van den Brink & Van Ree, 2003).

A number of reviews have demonstrated the positive effect of the Community Reinforcement Approach (CRA; Finney & Monahan, 1996; Holder et al., 1991; Miller et al., 1995, 1998 and 2003; Miller & Wilbourne, 2002). CRA and CRA components have been placed high on the list of strongly supported treatment methods for alcohol problems. These outcomes provide consistent empirical evidence for the value of CRA.

A short overview based on Carroll (1998, p. 8-12) is provided in the next section to illustrate several psychosocial interventions used in the management of addiction.

1.4.1. Psychosocial relapse prevention strategies

Psychosocial relapse prevention treatments are conducted in inpatient or residential programs, such as therapeutic communities, and in outpatient programs, such as intensive or minimal interventions. The contents of these programs are often based on interventions such as Twelve-Step Facilitation, Interpersonal Psychotherapy, Motivational Interviewing and Cognitive Behavioral Therapy (Project MATCH Research Group, 1997). These general programs are used to treat a variety of substance use disorders.

Twelve-Step Facilitation

Twelve-Step Facilitation (Nowinski et al., 1992, 1994) views problematic alcohol use as a behavioral, cognitive, spiritual and medical disease. In general, Twelve-Step Facilitation consists of a brief, structured, and manual-driven

approach provided on an individual basis in 12 to 15 sessions, to facilitate recovery from substance use disorders. Next to abstinence, a principal objective of Twelve-Step Facilitation is to mobilize the participant's commitment to and participation in Alcoholics Anonymous or related fellowships for other substances than alcohol. Participants are stimulated to attend self-help meetings and to document their Alcoholics Anonymous attendance and participation (Project MATCH Research Group, 1993).

The disease-model approaches consider substance use disorders as a disease that can be controlled but never cured. The emphasis in these disease model approaches is on patients' loss of control over substance use and other aspects of their lives. Similarly, the major change agent in disease-model approaches is involvement with Alcoholics Anonymous and learning to cope with nearly all drug-related problems by going to meetings or deepening involvement with fellowship activities.

Twelve-Step Facilitation may also be clinically useful (Project MATCH Research Group, 1997) in combination with additional pharmacotherapy such as disulfiram aimed at total abstinence (Carroll et al., 2000).

Interpersonal Psychotherapy

Interpersonal Psychotherapy (Rounsaville & Carroll, 1993), also known as Supportive-Expressive Therapy (Luborsky, 1984), “is based on the concept that psychiatric disorders and substance dependence are related to disorders in interpersonal functioning, which may be associated with problems such as substance use disorders. Interpersonal Psychotherapy has four distinct characteristics: (1) adherence to a medical model of psychiatric disorders, (2) focus on patients' difficulties in current interpersonal functioning, (3) brevity and consistency of focus, and (4) use of an exploratory stance by the therapist that is similar to that of supportive and expressive therapies” (cited from Carroll, 1998, p 11). In the more exploratory short-term dynamic Interpersonal Psychotherapy approaches, substance use is viewed as a symptom of other difficulties and conflicts. Interpersonal Psychotherapy focuses less directly on the use of substances than suggested in concurrent psychosocial therapies. Interpersonal

Therapy can be combined with pharmacotherapy (c.f. Weissman, Klerman, Prusoff, Sholomskas, & Padian, 1981) and may be both viable and effective in the treatment of substance use disorders (Carroll, Rounsaville & Gawin, 1991).

Cognitive Behavioral Therapy

Cognitive Behavioral Therapy encompasses a wide range of cognitive and behavioral treatments, all of which perceive substance dependence to be understandable in terms of its antecedents and consequences (Carroll, 1998, p. 8). Cognitive Behavioral Therapy includes the Community Reinforcement Approach (CRA; Meyers & Smith 1995), Beck's Cognitive Therapy (Beck et al., 1991) and Marlatt's Relapse Prevention (Marlatt & Gordon, 1985).

Cognitive therapy "is a system of psychotherapy that attempts to reduce excessive emotional reactions and self-defeating behavior by modifying the faulty or erroneous thinking and maladaptive beliefs that underlie these reactions" (Beck et al., 1991, p. 10, cited from Carroll, 1998, p. 9). In cognitive therapy, the therapist's approach to focus on cognitions is Socratic and based on leading the patient through a series of questions. The treatment is believed to reduce substance use by helping the patient change the way he or she thinks.

Cognitive Behavioral Therapy "differs from cognitive therapy primarily in terms of the emphasis on identifying, rather than understanding and changing, underlying beliefs about the self and the self in relationship to substance dependence as a primary focus of treatment. In Cognitive Behavioral Therapy, initial strategies stress behavioral aspects of coping (e.g., avoiding or leaving the situation, distraction, etc.) rather than "thinking" one's way out of a situation" (Carroll, 1998, p. 9). The accent is on self-control strategies, to recognize the processes and habits that underlie and maintain substance use and determine what can be done to change them.

Cognitive Behavioral Therapy can be combined with pharmacotherapy (Carroll et al., 2004; Mattick et al., 2003). When used in combination with medication, the scope of Cognitive Behavioral Therapy interventions expands to include a focus on enhancing medication compliance, such as medication response and monitoring compliance during sessions. There is evidence that Cognitive

Behavioral Therapy is an effective treatment to modify substance-using behavior (Baker et al., 2001; Carroll, 2000, Covi et al., 2002, Mattick, Ward & Hall, 1998; Maude-Griffin et al., 1998; Monti, et al., 1997; Rigter et al., 2004).

Motivational Interviewing

As outlined, Motivational Interviewing is a crucial intervention to use at the beginning of treatment and can subsequently be employed through the whole treatment. In the course of Motivational Interviewing, the subject may start pharmacotherapy to increase the probability that abstinence can be maintained (De Wildt et al., 2002). By using Motivational Interviewing techniques, the patient shifts through distinct stages (pre-contemplation, contemplation, preparation and action), where, in the preparation stage, plans can be made for additional pharmacotherapy when necessary or indicated. Motivational Interviewing can also lead to the application of coping skills training based on Cognitive Behavioral Therapy (Marlatt & Gordon, 1985), which maintains that learning and practice of specific substance-related coping skills fosters abstinence. There is cumulating evidence that Motivational Interviewing is an effective treatment strategy and is also cost-effective (Burke, Arkowitz & Menchola, 2003; Dunn, Deroo & Rivara, 2001; Holder et al. 2000; Rigter et al., 2004).

1.4.2. Pharmacological relapse prevention strategies

Pharmacological strategies to prevent relapse are not available for every substance use disorder. Adequate evidence based pharmacological intervention are currently not available for the treatment of cocaine dependence (de Lima et al., 2002) or amphetamine addiction (Srisurapanont et al., 2001). However, effective interventions are available for alcohol and opioid dependence. The pharmacological treatments can be divided into three main strategies (Health Counsel of the Netherlands, 2002a):

1 To *diminish the positive reinforcing effects* of the substance. This can be achieved by the administration of (high doses) of an agonist (e.g. methadone), partial agonist (e.g. buprenorphine) or antagonist (e.g.

naltrexone) in the treatment of opiate dependence. These agents occupy or block the receptor site, thereby discouraging substance use. With cure as the treatment goal and relapse prevention of all opioid use as an intermediate goal, only opioid antagonists are relevant, i.e. naltrexone.

2 To *reduce craving*. Some pharmacological agents have been associated with the reduction of craving, such as acamprosate and naltrexone in the reduction of alcohol craving;

3 To *initiate an aversive reaction* in case substance use is resumed, e.g. disulfiram in the treatment of alcohol dependence.

Naltrexone

For both the treatment of opioid and alcohol dependence, naltrexone appears to be an effective treatment. Naltrexone, an opioid antagonist, blocks the intrinsic properties of psychoactive substances, which act on the opioid receptor sites by competitively occupying these, and thereby promotes abstinence. However, despite the demonstrated pharmacological properties, there is limited legitimacy for the use of naltrexone in maintenance treatment of detoxified patients with opioid use disorders since treatment compliance is generally low resulting in high relapse rates (Kirchmayer et al., 2002; Roozen et al., 2002). The induction of naltrexone through a rapid detoxification procedure might increase the efficacy of naltrexone in a maintenance program (O' Connor & Fiellin, 2000).

In the treatment of alcohol disorders it has repeatedly been found that naltrexone is more favorable in terms of relapse rates and percentage of drinking days than placebo (Roozen et al., 2002). Therefore, naltrexone is regarded as an effective adjuvant therapy for alcohol dependence in adults (Bouza et al., 2004).

Acamprosate

Another treatment option for patients with alcohol problems is acamprosate (see also Bouza et al., 2004). Acamprosate is thought to reduce craving that is often experienced by patients with alcohol use disorders. The specific mechanism of action is not fully understood, because it is a small flexible molecule with similarities to several neuro-active amino acids and is used in high doses

(Littleton & Zieglgansberger, 2003). All these factors suggest that it may have multiple actions. The effects of acamprosate seem to be that it inhibits the glutamatergic transmitter system involved in both the negative reinforcing effects of alcohol and the conditioned "pseudo-withdrawal" associated with cue-induced relapse (Littleton & Zieglgansberger, 2003).

Reviews have yielded strong evidence that acamprosate is more effective than placebo (Garbutt et al., 1999; Miller & Wilbourne, 2002). This finding was also replicated in a recent trial (Kiefer et al., 2003) investigating the single and combined effects of acamprosate and naltrexone in alcohol dependence. It has been shown that the addition of naltrexone to acamprosate is more effective than placebo or acamprosate alone.

Disulfiram

Controlled clinical trials have shown inconsistent results regarding the effectiveness of disulfiram. Disulfiram inhibits aldehyde dehydrogenase, leading to elevations in acetaldehyde levels after ethanol consumption. This increase in acetaldehyde levels produces adverse experiences as a result of a variety of physiological effects, such as nausea, hypotension and flushing.

A recent review yielded limited evidence for the use of disulfiram for the decrease of drinking frequency (Garbutt et al., 1999). There is also little evidence for improved continuous abstinence rates (Garbutt et al., 1999). However, supervised disulfiram administration might be an effective method to enhance compliance, which is often poor (see Brewer, 1993; Fuller & Gordis, 2004). There is also some evidence for the effectiveness of the combination of acamprosate and disulfiram in the treatment of alcohol dependence (Besson et al., 1998; Fuller & Gordis, 2004; Wilde & Wagstaff, 1997).

Bupropion

In the treatment of smoking cessation, antidepressant medications (bupropion, nortriptyline) have proven to be effective, but the effect size is modest at best - just as with the anti-heroin and anti-alcohol medications- (Hughes, Stead & Lancaster, 2003). Another possible treatment option for the treatment of nicotine

addiction is the use of opioid antagonists such as naltrexone, which may attenuate the reinforcing effects of nicotine (David, Lancaster & Stead, 2003).

1.5. Integration of pharmacological and psychosocial treatments

The effect size of most studies of pharmacological interventions is rather modest, partly because of limited treatment compliance. In the early history of medicine, Hippocrates (c.460-377BC) admonished physicians to be alert to patients' compliance with medical regimens (Hippocrates, *On Decorum,* translation, 1923). Unfortunately, current pharmacological interventions still generally suffer from poor compliance (McLellan & O'Brien, 1996).

To increase the effect sizes of pharmacological agents, efforts to improve compliance are pivotal in substance abuse treatment (McLellan & O'Brien, 1996). Consequently, research should pursue improvement of sustained release formulation or longer-acting forms of these agents, such as implants or injection depots. In the search for new strategies, a new viable treatment option may be the use of vaccines, by inducing drug-specific antibodies in the bloodstream that bind to the drug of abuse and prevent its entry into the brain (Kantak, 2003). But even this innovative approach is only likely to work with individuals who are highly motivated to stop using drugs altogether and as part of a comprehensive treatment program (Kantak, 2003). Integrated treatments have, therefore, become an important focus for clinical research and will probably include biological, behavioral, and social-context components (Leshner, 1997).

In this respect, several new and evidence-based psychosocial interventions have been mentioned in the contemporary literature (Miller et al., 2002) in which pharmacological components can be integrated to create a multi-modal treatment package (Carroll, 1998; Carroll et al., 2004; O'Malley 1996). For example, nicotine replacement therapy combined with additional support has been promulgated in the contemporary literature (Hughes et al., 1996; Law & Tang, 1995; Mooney & Hatsukami, 2001).

Despite the use of combined and integrated forms of pharmacotherapy and psychotherapy in general addiction treatment services, the added value of these combinations is not well studied (Kranzler, 2000). Combination therapy in the treatment of alcohol dependence has been less successful with no obvious advantages or added value of psychosocial interventions when combined with acamprosate (De Wildt et al., 2002). In addition, the evidence is scant with regard to the type and intensity of psychosocial treatment that should be combined with the medication to optimize its efficacy (Pelc et al., 2002; Soyka et al., 2002).

1.6. The Community Reinforcement Approach as an integrative treatment

A form of treatment that creatively combines psychosocial and pharmacological approaches is the Community Reinforcement Approach (CRA). In search of an innovative approach to reduce an individual's alcohol problem and departing from Skinner's operant learning paradigm, Nathan Azrin and George Hunt composed this treatment form in the early seventies. CRA is propagated as an integrated therapy that focuses on the reinforcement of an alternative lifestyle that is more rewarding than substance use (Meyers & Smith, 1995). The treatment stratifies environmental contingents to pursue non-substance-using behavior, by enhancing and supporting the subject's ability to cope with several major life-areas. Primarily, CRA does not address directly internal psychological changes, but focuses on environmental contingencies. The first trials were conducted to assess the efficacy of their intervention (e.g. Hunt & Azrin, 1973). In the second CRA trial (Azrin, 1976), disulfiram was added to the CRA treatment. In addition, a concerned significant other was utilized to monitor compliance with the medication regimen. The involvement of a concerned other was also utilized to influence the subject to increase both the quality of life of the subject and the concerned significant other. The form that is best known now is the one described by Meyers and Smith (1995). They introduced aspects from Motivational Interviewing (Miller & Rollnick, 1992) and coping skills (e.g. Marlatt & Gordon,

1985). CRA pays attention to coping skills (e.g. substance refusal skills), social skills (e.g. communication skills), vocational skills (e.g. job-club), reciprocal marital counseling (e.g. the concerned significant other reinforces non-substance use with concomitant behavior which the subject appreciates (and withholds rewards when substance abuse occurs), and recreational elements (e.g. leisure time)).

Stephen Higgins (Higgins et al. 2004) has extended CRA with a formal, laboratory controlled contingency management component: tangible or contrived reinforcers (vouchers) are provided to initiate and maintain abstinence for cocaine dependent individuals. These vouchers are redeemable for items consistent with a drug-free lifestyle and are contingent upon the patient's provision of drug-free urine toxicology specimens.

CRA is regarded to be an effective approach (Miller et al., 1995, 1998 and 2003; Miller & Wilbourne, 2002). Nevertheless, the use of CRA has been limited in general practice.

1.7. Limited dissemination of CRA

As outlined above, CRA is regarded as a multi-modal biopsychosocial treatment, which consists of of multiform evidence-based components. Despite the description by Meyers and Smith (1995), CRA leads to misconceptions. Many researchers consider CRA as an expanding concept consisting of a variety of approaches, which causes doubts about the content and method of CRA. For example, one of the promoters of CRA often encounters misconceptions, in which it is assumed that Higgins' vouchers are being considered as CRA in and of themselves. Other people assume that CRA is similar to Motivational Interviewing simply because they hear about getting behavior change without confrontation (Smith, 2003). It seems that the variations in the description of the method and content of CRA have created confusion about, and a disinterest in, the method among many clinicians.

Despite the success of CRA, for many years the CRA methodology was only accessible to a few researchers (Miller & Meyers, 2002, p. 165). Until a couple of years ago there was no CRA manual available with adequate descriptions of the approach, and video's or trained clinicians who organized workshops to promote CRA were non-existent (Miller & Meyers, 2002, p. 166). In addition, research outside the USA has been virtually absent, which has compromised the availability of CRA promoters in Europe.

Another reason why CRA is hardly applied might be the inclusion of interventions such as home visits to search for natural rewarding resources contingent on positive environmental reinforcement, to foster abstinence. To implement this method in routine practice might be regarded as too time consuming and labor intense. Most treatment modalities do not attend to social reinforcement of environmental contingencies.

CRA's historical development, the inclusion of several therapeutic interventions, the intensity and duration, it's reported effectiveness, the compatibility with the pharmacological approach and possible misconceptions, all speak to the need for scientific evaluation of the concept and its effectiveness for the treatment of alcohol, opioid, tobacco and cocaine dependent patients.

1.8. Research Questions

The available evidence and, in contrast, the limited dissemination and implementation of CRA in clinical routine practice warrants investigation of CRA. Although several reviews have outlined its benefit in terms of the cost-effectiveness of CRA in the treatment of problematic alcohol using patients (Wolfe & Meyers, 1999), studies of the treatment effectiveness of CRA, without a contingency management approach (vouchers), for patients with substance dependence is rather scant. Another limitation concerns the methodology of the seminal conducted studies. Poor methodology with an overestimation of the effect might be partially responsible for the initial impressive effects. To our knowledge,

most of the reviews regarding the effectiveness of CRA have not appraised the effectiveness of CRA when compared to treatments such as usual care, in a broad variety of addiction types.

In addition, current reviews do not address CRA integrated with pharmacological agents other than disulfiram or methadone. In the treatment of opioid and alcohol use disorders, naltrexone constitutes a viable option, compared to other available agents aimed to prevent relapse. In addition, data about the effects of CRA combined with naltrexone are absent. Therefore the following questions were formulated:

1. Is CRA, with and without pharmacotherapy, effective in the treatment of alcohol, opioid, tobacco and cocaine dependence? (*Chapters three, five, six, and seven*);
2. What is the (incremental) effectiveness of naltrexone in the treatment of alcohol and opioid use disorders? (*Chapter four*);
3. What is the conceptual and empirical content of CRA? (*Chapter two*).

1.9. Dissertation outline

In *Chapter two*, a conceptual and empirical analysis of CRA is given. In contemporary literature, the term Community Reinforcement Approach is used for an array of interventions. Pertaining to the promise of the many reports and the high rankings of CRA in several meta-analyses (Miller et al., 1995, 1998 and 2003; Miller & Wilbourne, 2002), it seems worthwhile to identify which elements of the CRA approach are currently being used. Therefore, the array of interventions used within the CRA framework in the contemporary literature is examined and outlined.

In *Chapter three* a systematic review of the effectiveness of CRA in the treatment of alcohol, cocaine and opioid dependence is conducted. The rationale is based on the fact that the cost-effectiveness of CRA has placed it high on the

list of strongly supported treatment methods for alcohol problems (Wolfe & Meyers, 1999). Furthermore, CRA has been applied in the treatment of a broad variety of substance use disorders other than alcohol dependence, e.g. cocaine and opioid dependence. Nevertheless, systematic reviews or meta-analyses, in which the effectiveness of CRA is compared with usual care, are scant. This review is conducted within the Cochrane Collaboration Review Group framework, with the objective to determine whether CRA therapy is more effective than usual care for alcohol, cocaine and opiate addiction.

In *Chapter four* another systematic review is conducted to summarize and update the evidence on the effectiveness of naltrexone (Gonzalez & Brogden, 1988) in the maintenance treatment of opioid and alcohol use disorders. Systematic reviews and meta-analyses have been published on the effectiveness of naltrexone in the treatment of alcohol dependence (Srisurapanont & Jarusuraisin, 2005) and naltrexone maintenance in opioid dependent patients (Kirchmayer et al., 2003). The review aims to study the effects of naltrexone compared to placebo in the maintenance treatment of opioid and alcohol dependence and to study the added value of naltrexone when combined with psychosocial treatment.

In *Chapter five* empirical data are provided concerning CRA combined with naltrexone in the treatment of opioid-dependence. In this study, the effects of naltrexone maintenance treatment on addictive behaviors and the predictive value of psychiatric comorbidity are described, and contrasted with a randomly drawn reference group, consisting of patients participating in a standard methadone program.

In *Chapter six*, the relatively new development of antagonists-accelerated opioid detoxification, with or without general anesthesia, is investigated. Following naltrexone-assisted detoxification, naltrexone maintenance treatment in combination with CRA was tested in the so-called EDOCRA[1] study. By means of a naturalistic design employing a follow up of 16 months after detoxification, addictive behaviors, craving, health, and quality of life are evaluated.

In *Chapter seven* the effects of naltrexone with Transdermal Nicotine Patches combined with or without CRA in a smoking population of recovered spontaneous pneumothorax patients is explored. Smoking is associated with many serious health problems such as cancer and coronary and cerebrovascular heart diseases. Another smoking-related condition is spontaneous pneumothorax. Preliminary evidence suggests that long-term exposure to cigarette smoke is associated with alterations in the responsivity of the endogenous opioid system and the hypothalamic-pituitary-adrenal axis that may contribute to the development of nicotine dependence (Krishnan-Sarin, Rosen & O'Malley, 1999). Several studies have suggested involvement of the opioid system and that naltrexone might have an effect on nicotine craving (Brauer et al., 1999, Hutchison et al., 1999, Wewers et al., 1998).

Transdermal Nicotine Patches are used concomitantly to attenuate nicotine withdrawal by tapering the nicotine level. These biological interventions are integrated in CRA, which focuses on improving the psychosocial conditions of patients with substance use disorders by increasing motivation, enhancing therapy attendance and skills training. In addition, social support and increasing self-efficacy are important contributions for long-term cessation (Breteler, Schotborg & Schippers, 1996). The aim of this chapter is to investigate the effects and feasibility of this new combination therapy in terms of craving and abstinence.

Chapter eight provides a concise summary, discusses the results and provides recommendations for further research and future treatment strategies.

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CHAPTER 2

Community Reinforcement Approach in treating addiction: a conceptual and historical analysis

Abstract

The Community Reinforcement Approach (CRA) ranks high as an effective treatment in the management of addictive disorders. CRA treats substance abuse behavior by modifying positive reinforcements in the individual's community context, and through behavioral skills training. Which components exactly produce CRAs' effectiveness is not fully clear, since the label has been used to cover a variety of procedures. This study examines the content of CRA and its development. We describe and tabulate components used within the CRA framework as they appear in treatment studies. A computerized literature search identified 15 protocols. These were unbundled resulting in a broad spectrum of CRA components. Recent studies varied in the number of components. The complexity of CRA has obscured the mechanism of treatment actions. Dismantling studies to assess the auxiliary value of each component, within the CRA framework, are recommended.

2.1. Introduction

Since 1973 when Hunt and Azrin (Hunt & Azrin, 1973) introduced the Community Reinforcement Approach (CRA), the intervention has been shown to be effective according to reviews of the treatment-outcome literature (Finney & Monahan, 1996; Holder et al., 1991; Miller et al., 1995, 1998 and 2003; Miller & Wilbourne, 2002). CRA considers substance use disorders as behaviors that can be modified by positive reinforcement in the individual's natural environment. According to this model, sampling and practicing alternative rewarding activities in the community are essential to initiate and maintain abstinence (Schottenfeld et al., 2000).

Hunt and Azrin based the CRA on the operant learning theory postulated by B.F. Skinner (Skinner, 1938). Knowledge of how the environment interacts on the organism is essential to manipulate the environmental context of behavioral events, as the events themselves cannot be influenced (Hayes, Barnes-Holmes & Roche, 2001).

The reinforcing effect of substance use can interfere with concurrent normal reinforcers producing a postponement or omission in the distribution of these positive reinforcers. As Hunt and Azrin, state, "pleasant social interactions and individual recreational activities cannot be performed satisfactorily, if at all, when one is an alcoholic" (Hunt & Azrin, 1973, p. 92). The following consequences of substance use have been identified: (1) the negative interference of substance use leading to a loss of engaging rewarding activities as a result of a time-out. This is caused by the delay in engaging in rewarding activities resulting in a decrease of power of these normal reinforcers; (2) The intrinsic reinforcing effects of substance use, which have the potential to corrupt, and eventually, to supplant the sampling and the performance of rewarding activities.

Therefore, CRA attempts to modify substance abuse by increasing normal positive reinforcement from areas such as vocational, familial and social, to compete with the reinforcing effects of substance use (c.f. Azrin, 1976).

Recent research has confirmed an inverse relationship between substance use and substance–free activities (Correia, Benson & Carey, 2005). Reinstalling

the reinforcing power of personal activities and manipulating the delay and time-out of positive reinforcements (Holz & Azrin, 1963) is fundamental in the unifying CRA concept. "Consequently, for maximum effectiveness of this time-out dimension, the normal reinforcers should be grouped closely together in time, as well being of qualitatively great value" (Hunt & Azrin, 1973, p. 92).

CRA stems from the community mental health approach, which suggests that mental disorders are influenced by forces induced in and maintained by the community (Hunt & Azrin, 1973). By focusing on environment-organism interactions, Hunt and Azrin designated an adaptation of this approach to treat alcohol abuse, called "community-reinforcement approach to alcoholism" (Hunt & Azrin, 1973, p. 92.).

Recent CRA versions include social skills training, stress management training, cognitive modifications, relapse prevention (Meyers & Smith, 1995), and motivational interviewing (Miller et al., 1999a). Moreover, the role of medication in CRA has evolved over the years. In the beginning, no medication was involved. Later, disulfiram was introduced, and still later, methadone, naltrexone, and buprenorphine became part of the treatment.

CRA has been applied to a variety of substance use disorders other than alcohol abuse and dependence, such as cocaine dependence (e.g. Higgins et al., 2003), opioid addiction (e.g. Abbott et al., 1998a), and nicotine dependence (Roozen et al., accepted). Although almost all studies have aimed at abstinence as the treatment goal, other options, like stabilizing and controlling use, i.e. harm prevention, are also targeted as a treatment goal.

Since the original presentation, a variety of protocols on CRA have been developed and different manuals have been published. This study aims to identify the core components of CRA and investigates whether there is an evolution in the content of CRA. This could help in clarifying the active components and their mechanisms of change, which is the key to the continued refinement of psychosocial treatments (McCaul & Monti, 2003). The objective is to examine and outline the array of interventions that have been applied in studies evaluating the effects of CRA, and to analyze the components of CRA conceptually and historically.

2.2. Methods

2.2.1. Search strategy

A computer search was done on the following databases: Biological Abstracts, ERIC, LISA, MEDLINE, OSH, Periodical Abstracts, PsycINFO, SERFILE, Sociological Abstracts, EMBASE and CINAHL. All databases were searched from the date of commencement of the beginning of each database. The search was conducted in March 2002, using the search strategy of the UK Cochrane Center (October 1996), based on the first two stages of the Medline search strategy recommended in the Cochrane Handbook (Appendix V of Section V) published by Dickersin et al. (1994). This was run in conjunction with a specific search that included combinations of the following keywords: alcohol abuse, substance abuse, drug abuse, alcohol(-) related disorder(s), opioid(-)related disorder(s), opiate(-)related disorder(s), cocaine(-)related disorder(s), community reinforcement approach, community reinforcement, CRA, disulfiram, acamprosate, methadone, heroin, naltrexone and buprenorphine. The selection involved a screening of the Cochrane Library, 2002, issue 1, and a relevant reference search in all identified articles, manuscripts and chapters about CRA.

2.2.2. Criteria for considering studies

Types of studies. Randomized controlled trials (RCTs), clinical controlled trials (CCTs), matched controlled trails, naturalistic design studies, single-group studies and pilot studies were included. To avoid clinical heterogeneity and to prevent intervention descriptions that might cause bias, case reports or studies with a very small sample size ($n < 5$) were excluded. We focused on the content of CRA, regardless of the effects of the protocols.

Types of participants. Studies with subjects with alcohol, cocaine and opiate abuse or dependence (DSM-IV) between 18 and 65 years of age were included.

Types of interventions. Studies that labeled their intervention as CRA were included whether or not combined with pharmacological agents (e.g. disulfiram) or other operant approaches, such as voucher-based contingency management. Treatment-packages based on CRA behavioral components (Azrin et al., 1994), which encompass multiple components such as a social-club with social/recreational activities (Mallams et al., 1982), reciprocity counseling/behavioral marital therapy (Azrin, Naster & Jones, 1973; Azrin, Nunn & Frantz, 1980; Azrin et al., 1981), Job Club (Azrin & Besalel, 1980, 1983; Azrin, Flores & Kaplan, 1975; Azrin & Philips, 1979; Azrin et al., 1981), family-member involvement (Sisson & Azrin, 1986) and vouchers (Higgins et al., 2003) were included. Studies were included in which a description and/or reference was given regarding the intervention components.

2.2.3. Data extraction

From the method section of the included studies, data was extracted on CRA treatment components. These components were stratified according to type of substance, setting, goal of treatment, and pharmacological support (Table 2.1).

2.3. Results

2.3.1. Studies identified

The search identified 66 references via PsycINFO, 90 references via MEDLINE, 24 via EMBASE and 2 via CINAHL. Consulting the additional databases, Biological Abstracts, ERIC, LISA, OSH, Periodical Abstracts, SERFILE, Sociological Abstracts and the Cochrane database, yielded 97 different references. After deleting duplicates from all the databases consulted, 167 unique references remained.

The first selection was based on titles, keywords and abstracts, and resulted in selecting 26 empirical studies in which CRA was (one of) the treatment(s) and rejecting 141 studies.

Five of the rejected empirical studies reported on Community Reinforcement and Family Training (CRAFT). CRAFT, focusing on family members, was developed on the assumption that concerned others can help to persuade resistant substance abusers to seek treatment (Meyers, Miller & Smith, 2001). Because of this different focus, CRAFT studies were not considered to be within the scope of this conceptual analysis and were thus discarded.

Of the selected 26 studies, three studies were considered as case reports or case studies and were excluded (Budney et al., 1991; Fix, 2001; Vick & Houden, 1991).

Three additional studies were identified through reference checking (Azrin et al., 1994, 1996; Mallams et al., 1982). Thus 26 empirical CRA studies remained. These 26 studies were pared down further as follows.

Three studies (Higgins et al, 1995; 1997; 2000(b)) were follow-up studies of earlier publications and reported on the same treatment protocol (Higgins et al., 1993; 1994; 2000(a)). Two studies reported on the same trial in substance abusers (Azrin et al., 1994, 1996) and another four studies reported on the same two alcohol trials (Miller et al., 1992; Miller et al., 2001a,b) and homeless people (Smith et al., 1998; Smith & Delaney, 2001). The study of Abbott et al. (1999) was based on the same data-set as Abbott et al. (1998a), comparing subjects who had entered a program with or without methadone as transfers from other community methadone programs without the use of CRA and was therefore excluded. The study on AIDS risk behavior (Abbott et al., 1998b) was based on Abbott et al. (1998a). Both were counted as one study. Miller et al. (2001a,b) consisted of 2 complementary chapters (2 search hits) and were therefore considered as one trial in this conceptual analysis. The study of Mallams et al. (1982) evaluated only one CRA aspect (social club) and was discarded. Additionally, the alcohol study from Miller et al., (1999b) conducted on Native Americans, at the Na'nazhoozhi Center in Gallup, New Mexico, blended CRA with motivational interviewing, and traditional native spirituality (Miller, 2003) and was

therefore left out in this analysis. At the end of this process, 15 studies containing distinctive CRA treatment protocols were included.

2.3.2. Study characteristics

Alcohol. Six studies dealt with CRA in alcohol patients (Azrin, 1976; Azrin et al., 1982; Hunt & Azrin, 1973; Kalman et al., 2000; Miller et al., 2001a,b; Smith et al., 1998). The first two studies, which were the seminal studies for CRA as a treatment modality, were inpatient studies (Azrin, 1976; Hunt & Azrin, 1973). These were followed by an outpatient study (Azrin et al., 1982). The alcohol study carried out by Miller et al. (2001a,b) included two sub-groups: (1) disulfiram-eligible and (2) disulfiram-ineligible subjects. One alcohol study dealt with homeless alcohol-dependent subjects (Smith et al., 1998). Finally, one study reported on sociopathic alcoholics (Kalman et al., 2000).

Cocaine. Four studies (Higgins et al., 1991, 1993, 1994, 2000a) compared the effects of CRA with contingent and non-contingent 'incentives' on abstinence in the treatment of cocaine. The study of Higgins et al. (1994) investigated CRA without 'incentives'.

Opioids. Three studies dealt with the management of opioid addiction. One study (Bickel et al., 1997) evaluated the effect of a buprenorphine dose-taper combined with CRA and 'incentives'. Furthermore, one study investigated the effects of CRA in a rapid detoxification procedure and the effects of CRA combined with naltrexone maintenance aimed at abstinence (Roozen et al., 1997; see also Roozen et al., 2003). Another study (Abbott et al., 1998a) investigated the effects of CRA in a methadone maintenance program.

Multiple substances. Two studies focused on multiple substance use disorders. One study investigated CRA in a population with an opiate as well as a cocaine addiction (Schottenfeld et al., 2000). The study carried out by Azrin et al. (1994, 1996) included subjects with different substance use disorders.

2.3.3. Treatment protocols and manuals

The treatment methods in the early studies (Azrin, 1976; Azrin et al., 1982; Hunt & Azrin, 1973) constitute the initiation of CRA and can be considered as unique protocols. Because of overlap, we considered the treatment method described in Azrin, 1976 and Hunt & Azrin, 1973 as complementary to Azrin et al. 1982 (Azrin et al., 1982, Miller, 2001, p. 11). We considered Azrin et al. (1994) as a unique protocol. Many of the other studies described their treatment protocols rather briefly and referred basically to published manuals. The manuals that we found are those of Meyers and Smith (1995) and Budney and Higgins (1998).

Four studies referred to Meyers and Smith (1995) and were therefore considered as one group (Abbott et al., 1998b; Smith et al., 1998; Kalman et al., 2000; Roozen et al., 1997). The interventions conducted by Higgins et al. (1991, 1993, 1994, 2000a) were based on the manual by Budney and Higgins (1998). The CRA protocol of the study on opioids (Bickel et al., 1997) was based on Higgins et al., (1993), which is in turn connected to the cocaine manual (Budney & Higgins, 1998). The CRA description of Schottenfeld et al., 2000) refers explicitly to this cocaine manual and was also combined into one group. Eventually, 6 unique treatment protocols, presented as CRA, were included in this analysis (Table 2.1).

2.3.4. Treatment components

Studies differed in the number and the kind of interventions that they included as part of CRA. Some components were described as part of a more encompassing technique that is compartmentalized in our analysis. Relapse prevention, being a core element in the Meyers and Smith (1995) approach, incorporates components such as functional analyses, self-management planning, use of a significant other (i.e. early warning system), refusal training, problem solving, and cognitive modification. A functional analysis identifies triggers of potential high-risk situations and pleasurable non-substance using behaviors (Meyers & Smith, 1995).

Additionally, the procedure refers also to problem solving skills to introduce pleasurable activities that may replace substance-using behavior (Smith & Meyers, 2001, p. 35). From that perspective, there is an overlap with self-management planning, which focuses also on replacement of high-risk situations, by rearranging the environment into low-risk or safe situations (Budney & Higgins, 1998). Behavioral skill training (Meyers & Smith, 1995) covers a variety of components such as self-management planning, refusal training, problem solving, communication training, and cognitive modification.

Some components were not considered to be part of usual CRA per se (e.g. urine analysis review, i.e. progress graphs; Budney & Higgins, 1998; independence training; Meyers & Smith, 1995).

Unraveling the descriptions and reviewing the manuals and protocols resulted in the identification of the following 18 more or less discrete CRA components:

1. A *functional analysis* primarily examines the antecedents (external stimulus, cognitive reaction and concomitant affect) and consequences of a specific behavior of interest, such as substance abuse or the consumption of alcohol in specific potential high-risk situations (Azrin, 1976). In addition, CRA also focuses on a secondary functional analysis, which attempts to analyze pleasurable non-substance related behaviors (Meyers & Smith, 1995). Two CRA functional analysis forms have been developed: for drinking behavior (Meyers & Smith, 1995, p. 34-35) and for non-drinking behavior (Meyers & Smith, 1995, p. 38-39).
2. The *self-management planning* (Budney & Higgins, 1998, p. 63) or the related stimulus control procedure (e.g. Azrin et al., 1994; see also Azrin et al., 2001) addresses external stimulus situations that are precursors to drug use and high-risk social situations, to increase the amount of time spent engaging in drug incompatible and pro-social activities. A comprehensive Risk-List, regarding situations, persons and places associated with substance abuse and similarly situations incompatible or non-associated with drug use is created (Safe-List). Subsequently, a Daily Planner Recording Form is utilized to schedule these non-drug-

associated activities for the next day. In addition, the treatment plan is governed by assessment through the Happiness Scale and the Goals of Counseling Form (Smith & Meyers, 2001, p.44-47).

3. The *contingency management with vouchers* (Higgins et al, 2003) encompasses a reinforcement procedure in which points can be earned as rewards for non-using. Evidence is presented by examining the urine specimens collected. Earned points can be exchanged for retail items or services in the community.
4. *Involvement of the significant other* (Azrin 1976, Azrin et al., 1982), often a partner, spouse or friend to enhance compliance and adherence in treatment including pharmacological support, e.g. medication assurance procedure (Azrin 1976), and to create a monitoring system, e.g. early warning/mood monitoring (Azrin, 1976). Additionally, assistance can be obtained from the significant other to promote non-substance related activities, session attendance, providing transportation, reminders, and supervising assigned home practice (Azrin et al., 1994).
5. To address the adherence of a medication regime, CRA studies used a *disulfiram* or medication *assurance procedure* (Azrin, 1976, Azrin et al., 1982). Azrin added motivational procedures and psycho-education to improve adherence. Meyers and Smith (1995) enumerate ten advantages of being on disulfiram. A monitor ensured that daily doses of the prescribed medication were dispensed and used, to establish an antabuse habit (Azrin, 1976). The study of Azrin et al. (1982) added techniques by assisting the participant specifically to take a dose during the session. More recent studies incorporate agents including methadone, naltrexone and buprenorphine.
6. To observe subjects' vocational, recreational activities, and social interactions with spouses, partners and family to generate and improve existing environmental contingencies, *home visits* (Hunt & Azrin, 1973) can be made.
7. Job-finding or *vocational counseling* (Azrin, 1976; Hunt & Azrin, 1973) is employed to realize a satisfying, gainful employment or career activity,

which might be important to achieve and maintain abstinence. The procedures are based on those outlined in Azrin and Besalel's Job Club Counselor's Manual (1980). An early study on job-finding (Jones & Azrin, 1973) demonstrated that offering financial incentives to the public to report job openings that resulted in placement produced substantially more job placements than using employment agencies and other standard services, at about 20% of the cost.

8. The goal of a *social club,* including social counseling (Hunt and Azrin, 1973) or social club component of CRA (Meyers & Smith, 1995, p. 5) is to increase subjects' skill in handling interpersonal situations so they experience more positive reinforcement and less negative, aversive effect from social interactions (Monti et al., 1989). The social club (Azrin, 1976) gives subjects a practical opportunity to develop and practice new social skills and to create recreational activities in a non-threatening drug or alcohol free environment, similar to the one outlined by Mallams et al. (1982).
9. A related intervention, although not per se applied in a formal created context such as a social club, is *social/recreational counseling* to develop satisfying social and recreational activities that compete with alcohol use and support sobriety. The development of potentially reinforcing activities that subjects are interested in pursuing and creation of a list of persons who might participate in these activities is pivotal. Specifically, finding at least one safe (non-substance using) person has priority. However, some individuals have impaired access to recourses associated with non-substance related activities. Therefore Reinforcement-Access Counseling (Hunt & Azrin, 1973) was implemented to facilitate engagement (Priming) into positive, rewarding behavior (see also Budney & Higgins, 1998, p. 42). Also a buddy (Azrin, 1976), an abstinent former patient as a peer-advisor, can be implemented for participants with an impaired social network. Time management is introduced to plan and schedule events and activities so that little high-risk time is available. Planning and scheduling activities increase the likelihood that subjects will follow

through with treatment goals and activities. Azrin et al. (1994) added Behavioral Contracting to stimulate reinforcement contingent on drug incompatible activities (Azrin et al., 1994). Behavioral contracting or direct reinforcement (see also Contingency management) consisted of establishing responses such as focusing on employment (e.g. Azrin & Besalel, 1980, 1983), money management, and accompaniment to social activities by the spouse (i.e. specified on a Safe-List). The amount of time spent in Safe-Activities is monitored and reinforced.

10. In a specially devised form of *relaxation training* (Urge Control Procedure; Azrin et al., 1994; see also Azrin et al., 2001) subjects are taught to interrupt proprioceptive sensations (internal stimuli), urges, thoughts, and incipient actions associated with substance using behavior, and to replace these thoughts and sensations by competing thoughts and relaxation (e.g. Azrin, Nunn & Frantz, 1980).
11. Drink or *substance refusal training* (Azrin et al., 1982), is considered as a form of communication training in which participants are trained to be consistent about refusing alcohol or drugs, without making it into an issue (Sisson & Azrin, 1989).
12. Problem-prevention rehearsal (Azrin, 1976) or *problem solving* (D'Zurilla and Goldfried, 1971) is employed to teach strategies for handling daily hassles related to substance abuse (c.f. Azrin et al., 1994).
13. According to Miller (2001, p.22) *motivational counseling* was introduced by Azrin et al. (1982) to promote treatment retention. Motivational counseling encompassed an interview (Inconvenience Review Checklist) to capture salient reasons for treatment engagement and enhancement of self-motivation (i.e. Annoyance Review; Azrin et al., 1994) and to set positive expectations in social interactions with the participants.
14. To foster abstinence for an agreed-upon, limited time period, *sobriety sampling* (Azrin et al., 1982) was introduced. The process of negotiating is to settle upon an intermediate goal that appears to be a challenge, but one that is obtainable (see Miller & Page, 1991).

15. To increase positive communication between family members and to improve family relationships, *communication training* can be applied. The Perfect Relationship Form (Smith & Meyers, 2001, p. 57) is designed to explore the individuals' skill level. Another way to re-establish a relationship that favors pleasant events is to utilize the Daily Reminder to be Nice Form (Sisson & Azrin, 1989, p. 254-255; Meyers & Smith, 1995, p. 179). Three main communication procedures, to be used in family communication at home, were also modeled and practiced during session (Azrin et al., 1994; see also Azrin et al., 2001). These interventions include Reciprocity Awareness, Annoyance/Anger Prevention and Positive Request Procedure (Azrin et al., 1994).
16. Related to communication training, techniques to resolve marital conflicts arising from unrealistic expectations or attempts to control a partner's behavior through aversive means and inadequate communication were also developed. This focus is designated as *relationship counseling* (Budney & Higgins, 1998) or *reciprocal relationship counseling* (Azrin, Naster, Jones, 1973; Stuart, 1969) or *behavioral marital/family therapy* (Azrin, 1976; Hunt & Azrin, 1973) and also includes an early warning system (Azrin, 1976). This technique aims to enhance functioning as a marital partner, and makes substance abuse incompatible with the relationship. To explore the current state of happiness with the partner a Relation Happiness Scale (Azrin, Naster & Jones, 1973, p. 370) and a Perfect Relationship Form is used (Smith & Meyers, 2001, p. 57). To provide couples with examples of types of 'Relationship-Related Activities' a specific form developed by Azrin et al (1973, p. 371) can be administered. To resolve disagreement between the couple, a Reinforcer Sampling Principle (Ayllon & Azrin, 1968) can be employed.
17. Through *cognitive modification* the sampling of a rewarding lifestyle can be promoted (Miller & Meyers, 2001, pp.168). Cognitive modification is mentioned in the manual of Meyers and Smith (1995). Negative cognitive patterns lead to strong mood disturbances and anxiety, which in turn

compromise lifestyle development (see Meyers & Smith, 1995, p. 117-119).

18. To counter the increasing prevalence of HIV and Hepatitis B and C among injection drug users, interventions have been developed aimed at the reduction of risk-taking behavior (*HIV/ AIDS prevention*) such as injection drug use and high-risk sexual behavior (Abbott, 1998a).

2.3.5. Evolution of CRA

This study was not intended to evaluate the methodology and outcome of CRA. Elsewhere we concluded from such a review that CRA is more effective than treatment as usual when related to number of drinking days in subject with an alcohol use disorder. Moderate evidence is available that CRA with disulfiram is more effective related to number of drinking days and there is no difference for continuous abstinence. Furthermore, there is strong evidence that CRA with preferably abstinence-contingent incentives is more effective with regard to cocaine abstinence. Finally, there is limited evidence to support that CRA with incentives is more effective for opioid detox programs, and in methadone maintenance programs (Roozen et al., 2004).

In Table 2.1 the six identified CRA treatment protocols are ordered according to their year of publication and according to the CRA components they contain. The number of components of each protocol has been counted and is summated.

There is an increase in the number of components in the three seminal alcohol studies from 7 through 11 to 15, respectively, followed by an increase to 12, 15 and 17 in the last three groups of studies (Table 2.1).

In general, CRA is combined with a broad variety of pharmacological interventions (e.g. disulfiram, naltrexone, buprenorphine and methadone) in the treatment of a wide range of (multiple) substance use disorders. The first studies were aimed at stable abstinence, but CRA is currently also being employed in pursuit of stabilization and harm minimization (Abbott et al., 1998a,b). CRA has for the most part been applied in an outpatient setting.

Table 2.1. *CRA components used in CRA studies.*

Main intervention	Components	1973 Hunt & Azrin	1976 Azrin	1982 Azrin et al.	1994 Azrin et al.	1997 Bickel et al. 1991, 1993, 1994, 2000a Higgins et al. 2000 Schottenfeld et al.	1998a,b Abbott et al. 2000 Kalman et al. 2001a,b Miller et al. 1997 Roozen et al. 1998 Smith et al.
(Primary) substance		Alcohol	Alcohol	Alcohol	Cocaine/ opioid/cannabis	Cocaine/ opioid/cannabis	Alcohol/ opioid
Treatment goal	Abstinence	●	●	●	●	●	●
	Harm reduction / Stabilization						●
Setting	Inpatient	●	●				●[2]
	Outpatient			●	●	●	●[3]
Pharmacological support	Pharmaco therapy		●	●		●[1]	●
	1. Functional analysis		●	●	●	●	●
	2. Self-management planning		●	●	●	●	●
	3. Contingency management with vouchers					●	
	4. Involvement significant other	●	●	●	●	●	●
	5. Medication assurance procedure		●	●		●	●
	6. Home visits	●	●	●[4]			●
	7. Vocational counseling	●	●	●	●	●	●
	8. Social club	●	●	●	●	●	●
	9. Social / recreational counseling	●	●	●	●	●	●
	10. Relaxation training (Urge Control)			●	●	●	●
	11. Substance refusal training			●	●	●	●
	12. Problem solving		●	●	●	●	●
	13. Motivational counseling			●	●	●	●
	14. Sobriety sampling			●			●
	15. Communication skill training	●	●	●	●	●	●
	16. Reciprocal relationship counseling	●	●	●	●	●	●
	17. Cognitive modifications						●
	18. HIV /AIDS prevention					●	●
Number of components in protocol		7	11	15	12	15	17

Note: from all protocols only the first author is reflected. The dot (●) represent when a component is used. The Table displays the array of components used (bottom). [1]) Denotes that in the Higgins studies disulfiram was administered throughout the treatment when the subject met the DSM-III-R criteria for alcohol dependence. [2]) Denotes that the study of Roozen et al. (1997) conducted a rapid-detoxification in a semi-inpatient setting. [3]) Denotes that Smith et al. (1998) used a grant-supported apartment. [4]) Denotes that Azrin used home visits by counselors described in the section Recording procedures (Azrin et al., 1982, p.107).

2.4. Discussion

This conceptual and historical analysis of the components of CRA demonstrates that there has been a gradual increase in the number and content of treatment components applied in CRA-studies. The underlying operant reinforcement approach has been expanded to include new components over time, such as sobriety sampling, motivational counseling, cognitive modification, and skills training.

In general, CRA encompasses interventions aimed at behaviors that can be strengthened or weakened by their consequences (e.g. by having a subject participate in a rewarding activity) and interventions addressing the environment, such as an important significant other. Although CRA does not a priori endorse skills training, the CRA philosophy may assess the lack of necessary behavioral strategies and can govern the development of these coping-skills chosen from a menu of options or toolbox (Miller & Meyers, 2001, p. 169). The core and unifying principle is operant reinforcement (Skinner, 1938) and entails rewards that are consistently implemented contingent on defined stimuli in a broad variety of life areas.

Several reviews have shown that CRA packages are effective (Miller et al., 1995, 1998 and 2003; Miller & Wilbourne, 2002; Roozen et al, 2004). Nevertheless, the content of the included CRA studies varies substantially. The identified protocols sometimes use different terms (e.g. reciprocal relationship counseling or behavioral marital/family therapy) to cover comparable components. Consequently, it seems viable that the complexity, diverse content, and different terms used within CRA may have caused confusion, which negatively affects the likelihood of adopting CRA in routine practice.

This lack of consistency has also obscured the isolation of active components of CRA, resulting in a dearth of evidence about how CRA actually works. Some components have been highlighted individually or have been the subject of dismantling research. Some examples include a social-club with social /

recreational activities (Mallams et al., 1982), reinforcement of non-drug-related social, vocational, and recreational activities (Schottenfeld et al., 2000), reciprocity counseling (Azrin et al., 1973), Job club (Azrin, Flores & Kaplan, 1975; Azrin & Philips, 1979; Azrin et al., 1981), concerned other involvement and CRA pharmacotherapy–compliance procedure (Azrin et al., 1982; Sisson & Azrin, 1986), role of disulfiram within CRA (Miller et al., 2001ab) and incentives (Higgins et al., 2003; Jones & Azrin, 1973). Evidence about which components, and under which condition may be crucial to efficacy, let alone the differential weight of the combined components, is scant. There is an urgent need to establish a simplified and economical CRA, defined and driven by a unifying operant reinforcement framework.

In several trials, CRA has been employed in concert with a formal contingency management (voucher) component. The program was designed to maintain the power of contingencies, by managing the sampling, frequency and accuracy of administered and implemented contingencies in the patients' own community (Higgins, 2003). The success of operant reinforcement principles in the treatment of substance use disorders has been extensively illustrated (Higgins & Silverman, 1999; Higgins et al., 2003, Higgins, Heil & Plebiani Lussier, 2004). Nevertheless, the effects of voucher-based incentives often slowly dissipate after discontinuation. The effectiveness in the long term is probably dependent on the degree of non-substance abuse related reinforcement that occurs naturally in the community.

Studies of CRA show an increase in the inclusion of pharmacological agents. Agents such as buprenorphine, disulfiram, methadone and naltrexone directly compete with positive reinforcement induced by the use of alcohol and illicit substances. For instance, disulfiram therapy acts as a punisher of drinking and punishment is a behavioral process. “The efficacy of disulfiram appears to be at least as much behavioral as pharmacological” (Higgins, 2002). Another example is the prescription of naltrexone in alcoholics and opioid addicts, resulting in a reduction of the reinforcing properties of alcohol and heroin.

The present analysis has several limitations. The first limitation concerns the accuracy of the study details provided in Table 2.1. These details were derived

from the treatment descriptions explained in the method section of the published CRA papers. In general, these descriptions are brief, whereas a few components are explicitly mentioned, followed by a reference to one of the CRA manuals. Moreover, the differential weight of each component in the program was unclear. Furthermore, treatment descriptions might refer to procedures that were not necessarily attached to the CRA philosophy.

A second limitation of this study is the fact that several protocols used different terminology to classify more or less the same interventions. Based on interpretation we translated the interventions used in each protocol into discernible components as listed in Table 2.1. This might have led to some broad interventions such as CRA's relapse prevention becoming difficult to recognize in the list of components as reflected in Table 2.1.

A third limitation is that we omitted family-focused interventions, such as Community Reinforcement and Family Training (CRAFT), which are conceptually in alignment with the original CRA program. These interventions were developed with respect to the belief that family members can make helpful contributions to engage resistant substance abusers into treatment (Meyers, Miller & Smith, 2001; Meyers et al., 2002; Miller et al., 1999). Because of the primary focus on a concerned significant other (such as domestic violence prevention), instead of the focus on the individual with a substance use disorder, CRAFT studies were not considered within the scope of this conceptual analysis. However, several Azrin studies included compatible compliance procedures, and CRAFT studies have been also subject of updates and modifications. In our opinion this development related to CRAFT legitimizes it's own conceptual analysis.

A fourth limitation encompasses the notion that more recent version(s) of CRA have technically more components available. But technical availability does not necessarily mean that they were all being employed to treat each client. It depends on how the components are tailored to individual or population needs.

It is noteworthy that the evolution of CRA has not highlighted recent influences derived from operant research such as behavioral economics (e.g. delay discounting; see Bickel & Vuchinich, 2000). Clinical findings, derived from behavioral economics, should be incorporated into the CRA approach (Higgins,

2003). Studies of discounting or delayed consequences provide a scientific account in the prevention and treatment of substance use disorders (Higgins, Heil & Plebiani Lussier, 2004, p. 441).

Based on variables such as addiction severity and treatment stage, the core behavioral premises of CRA might be complemented with newer ones and which pharmacological agents from a menu of options, under the condition that the core CRA treatment remains uniform and parsimonious. The core CRA should be established by research aimed at the identification of CRA components, which are actually delivered in CRA, and based on whether or not they are having the postulated effects on in vivo contingencies. After clarifying the active components, research should focus on the mechanisms and mediators of behavioral outcomes (Pantalon et al., 2004). Therefore, further studies, which tease apart the components of CRA, are warranted.

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Acknowledgements

The Ministry of Health, Welfare and Sports (VWS) and (ZonMw) funded this project under grants 3100.0019. These agencies had no role in the conduct, interpretation, or analysis of the study. We would like to thank Mary Jansen for her comments on an earlier draft.

CHAPTER 3

A systematic review of the effectiveness of the Community Reinforcement Approach in alcohol, cocaine and opioid addiction

Abstract

The Community Reinforcement Approach (CRA) has been applied in the treatment of disorders resulting from alcohol, cocaine and opioid use. The objectives were to review the effectiveness of (1) CRA compared with usual care, and (2) CRA versus CRA plus contingency management. Studies were selected through a literature search of RCTs focusing on substance abuse. The search yielded 11 studies of mainly high methodological quality. The results of CRA, when compared to usual care: there is strong evidence that CRA is more effective with regard to number of drinking days, and conflicting evidence with regard to continuous abstinence in the alcohol treatment. There is moderate evidence that CRA with disulfiram is more effective in terms of number of drinking days, and limited evidence that there is no difference in effect in terms of continuous abstinence. Furthermore, there is strong evidence that CRA with 'incentives' is more effective with regard to cocaine abstinence. There is limited evidence that CRA with 'incentives' is more effective in an opioid detoxification program. There is limited evidence that CRA is more effective in a methadone maintenance program. Finally, there is strong evidence that CRA with abstinence-contingent 'incentives' is more effective than CRA (non-contingent incentives) treatment aimed at cocaine abstinence

3.1. Introduction

The Community Reinforcement Approach (CRA) is a biopsychosocial multifaceted approach to change a lifestyle of substance abuse. CRA acknowledges the role of environmental events and influences in habitual abuse, and focuses on alternative positive resources in the social environment (e.g. Meyers & Smith, 1995). CRA is based on the theoretical view that substance-related reinforcers and the relative lack of alternative reinforcers unrelated to substance abuse maintain dependence. In this view, the development of alternative rewarding social activities that are incompatible with substance use is essential to initiate and maintain abstinence (Schottenfeld et al., 2000).

Emphasis is placed on changing environmental contingencies in the aspects of life, such as labor, recreation, family involvement etc., to promote a lifestyle that is more rewarding than substance abuse. CRA integrates not only cognitive behavioral interventions, but also pharmacological interventions (e.g. disulfiram). Another operant method, which is widely applied in CRA research, involves voucher-based incentive programs to promote abstinence (Budney and Higgins, 1998). These vouchers are exchangeable for retail items or services, and can be obtained by an individual who has submitted substance-free urine samples.

Despite promising reports of early research (Azrin, 1976; Hunt & Azrin, 1973) on alcohol, CRA has not been widely implemented (Kadden, 2001). Possible reasons for this are the labor intensity and the relatively high costs (Barber, 1992). In spite of these reasons, the cost-effectiveness of CRA (Wolfe & Meyers, 1999) has placed it high on the list of strongly supported methods for the treatment of alcohol problems that are identified in structured reviews of the literature on treatment outcomes (Finney & Monahan, 1996; Holder et al., 1991; Miller et al., 1995, 1998, and 2003; Miller & Wilbourne, 2002). However, in general, these reviews contain only limited number alcohol studies involving CRA, mainly based on the early work of Azrin, which compromises assessments of effectiveness. Although the most recent review (Miller et al., 2003) contains also recent CRA trials. In addition, there seem to be no systematic reviews or meta-

analyses available in which the effectiveness of CRA, with or without voucher-based contingency management, is compared with usual care.

The objective of this systematic review was to evaluate the effectiveness of CRA in the treatment of alcohol, cocaine and opioid addiction. Comparisons that were made included:

1. CRA versus usual care;
2. CRA versus CRA plus voucher-based contingency management;
3. CRA versus CRA plus pharmacological support.

3.2. Method

3.2.1. Criteria for considering studies for this review

Types of studies Only (matched) randomized controlled trials (RCTs) were included.

Types of participants Subjects with alcohol, cocaine and opiate abuse or dependence (DSM-IV) between 18 and 65 years of age were included. RCTs with subjects whose substance dependence was not the main diagnosis, or whose addiction was not seen as a reason for contact, were excluded (e.g. subjects with a diagnosis of schizophrenia who also have a substance dependency).

Types of interventions Only RCTs that applied a behavioral approach based on CRA principles were included. RCTs in which only one component of CRA was investigated were excluded. RCTs in which a pharmacological agent (e.g. disulfiram) was administered, combined with psychosocial treatment based on CRA, were also included, as were RCTs based on CRA with pharmacological maintenance treatment (e.g. methadone).

Types of outcome measures Effectiveness was defined in terms of (1) (continuous) abstinence, determined by urine samples, blood samples or self-reports. When data on continuous abstinence were not available, abstinence percentages that imply abstinence percentages within a follow-up assessment period were included. Abstinence was regarded as a primary outcome measure in

maintenance treatment (e.g. methadone) pertaining to the cessation of illegal drug use (heroin). RCTs were included if at least one of the following outcome measures was used; (2) addiction severity, measured for example according to the ASI, a semi-structured interview that gives a multidimensional profile of the addicted individual and an indication of the addiction severity (McLellan et al., 1980). The ASI contains seven life domains (medical, employment, alcohol, substance, legal, psychiatric, family and social). The composite scores subsequently reflect the severity of each of the seven domains over the previous 30 days; (3) frequency of substance abuse, measured for example according to the number of (heavy) drinking days and time spent drinking; (4) time to relapse.

3.2.2. Search strategy for identification of studies

Relevant RCTs meeting the inclusion criteria were identified by:

1. A computer-aided search using two search engines: OVID and WebSPIRS. WebSPIRS was used for a search in the following databases: Biological Abstracts, ERIC, LISA, OSH, Periodical Abstracts, PsycINFO, SERFILE and Sociological Abstracts. OVID includes EMBASE, MEDLINE and CINAHL. All databases were searched from the date of commencement. The search was conducted in March 2002, using the highly sensitive search strategy of the UK Cochrane Centre (October 1996), based on the first two stages of the Medline search strategy recommended in the Cochrane Handbook (Appendix V of Section V) and published by Dickersin et al. (1994). This was run in conjunction with a specific search that included combinations of the following keywords: alcohol abuse, substance abuse, drug abuse, alcohol(-)related disorder(s), opioid(-)related disorder(s), opiate(-)related disorder(s), cocaine(-)related disorder(s), community reinforcement approach, community reinforcement, CRA, disulfiram, acamprosate, methadone, heroin, naltrexone and buprenorphine. Only RCTs that were published in the English language were included.
2. Screening references given in relevant identified trials and reviews.
3. Screening the Cochrane Library, 2002 issue 1.

3.2.3. Methods of the review

Study selection

Two reviewers (HGR and JJB) independently selected the trials to be included in the systematic review. As the reviewers were acquainted with the studies, these were not blinded with regard to author, journal or research center. Disagreements concerning the inclusion of RCTs were resolved by consensus. A third reviewer (MvT) was consulted if consensus was not achieved.

Methodological quality assessment

Two reviewers independently assessed the methodological quality of the RCTs. The criteria list (Table 3.1) that is recommended in the guidelines for systematic reviews issued by the Cochrane Back Review Group (van Tulder et al., 2003) was used, but adapted for this CRA review. The full criteria list with operationalization is available on request from the first author. The original criterion “blinding of care-providers” was omitted, because care-providers in the CRA studies could not be blinded for the treatment they provided. Two new items were added (items 9a and 9b in Table 3.1) in order to assess potential information bias. With regard to the primary effect measure, the results obtained by using standardized and valid measuring instruments, such as blood samples or urine samples give a higher validity of abstinence than self-reports. Furthermore, highly relevant assessments provide more information concerning the primary effect measure than secondary measurements, such as depression questionnaires.

Several external validity items were also added (Table 3.1). The items 10a, 10b and 10c were added, because a description of the content of the CRA program provides more clarity about what is actually tested and the extent to which the results can be compared to the findings of other studies. Furthermore, a clear explanation of the theoretical background of the experimental program was evaluated positively. ‘Treatment integrity’ influences the extent to which the results can be generalized and replicated. Item 12a indicates the level of experience of the therapists, and 12b indicates whether the therapists have been trained in the application of CRA. Specific training for the experimental program,

together with tape/video-recording to determine adherence (12c), increases the external validity of the study. Moreover, the effects of the administration of an experimental treatment can be improved when a protocol is used (12d).

An item was scored "positive"(+) if the criterion was fulfilled, "negative" (-) if it was not fulfilled, or "unclear" (?). A total score was computed by counting the number of positive scores, and high quality was defined as fulfilling 6 or more of the 11 internal validity criteria. If the article did not contain information about the methodological criteria, i.e. if one or more criteria were scored "unclear", the authors were contacted for additional information. Scores on the external validity criteria were considered as supplementary information, to give an indication of the extent to which the results of the studies could be generalized.

Data extraction

Two reviewers independently extracted the data concerning the following: study population (disorder, setting, gender and age, Addiction Severity Index composite scores, sample-size and dropouts), interventions (frequency and duration CRA and control group, interventions CRA) and results (follow-up results per outcome measure).

Data analysis

The data from the included studies were merged in a meta-analysis to quantify the effect. Separate meta-analyses were performed for the short (≤ 4 weeks), intermediate (> 4 and ≤ 16 weeks) and long-term (>16 and ≤ 24 weeks) effects of treatment (Van Tulder et al., 2003). When available, other and longer follow-up periods, up to one year are provided in Table 3.2 in the result section. The pooled Relative Risks (RR) were computed with 95% Confidence Intervals (CI) using the random effects model.

A qualitative analysis was also performed using a four-level rating system for the strength of the scientific evidence (Van Tulder et al., 2000):

Table 3.1. *Methodological quality assessment (adapted) of 11 studies on CRA in alcohol, cocaine and opiates addiction.*

	Internal validity criteria												**External validity criteria**											
First author, year	*1a*	*1b*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9a*	*9b*	ξ *int.*	*10a*	*10b*	*10c*	*11*	*12a*	*12b*	*12c*	*12d*	*13*	*14*	ξ *ext.*	ξ *int. + ext.*
Abott, 1998b	+	?	+	?	-	+	+	+	+	+	+	8	+	+	-	+	?	+	+	-	-	+	6	14
Azrin, 1982	+	-	+	+	-	-	+	+	+	-	+	7	+	+	+	+	+	+	-	+	-	-	7	14
Azrin, 1976	+	-	+	+	-	+	+	-	+	-	-	6	+	-	+	+	+	+	+	+	-	-	7	13
Bickel, 1997	+	-	?	?	-	-	+	+	+	+	+	6	+	+	-	+	-	-	-	-	-	+	4	10
Higgins, 1991	-	-	-	+	-	-	-	+	+	+	+	5	+	+	+	+	+	+	-	-	-	+	7	12
Higgins, 1993	+	+	+	+	-	-	+	+	+	+	+	9	+	+	+	+	+	+	-	+	-	+	8	17
Higgins, 1994	+	+	+	+	-	-	+	+	+	+	+	9	+	+	+	+	+	+	-	+	-	+	8	17
Higgins, 2000a	+	+	+	+	+	-	+	+	+	+	+	11	+	+	+	+	+	+	-	+	-	+	8	19
Hunt, 1973	+	-	+	+	-	+	+	-	+	-	-	6	+	-	+	+	+	+	+	+	-	-	7	13
Miller 2001a,b	+	-	+	-	-	+	+	+	+	+	+	8	+	+	+	+	-	+	-	+	-	+	7	15
Smith, 1998	+	+	+	+	+	+	+	+	+	+	+	11	+	+	+	+	+	+	-	+	+	+	9	20

Note: '+' reflects that the study met the criterion, '?' reflects that it was not clear if the study met the criterion, and ' –' reflects that a study didn't meet the criterion. A total score was obtained by summing the number of positive scored criteria. The following internal criteria were defined, 1a: Adequate randomization procedure; 1b: Concealment of treatment allocation; 2: Withdrawal/drop-out rate; 3: Co-interventions avoided or equal; 4: Blinding of patients; 5: Blinding of observer; 6: Intention-to-treat analysis; 7: Compliance; 8: Similarity of baseline characteristics; 9a: Validity of assessment; 9b: Relevance of assessment. The external criteria consisted of 10a: Description of CRA program; 10b: Description of usual care; 10c: Definition of CRA; 11: Follow-up; 12a: Experience; 12b: Training in CRA; 12c: Tape recording; 12d: According to CRA protocol; 13: Sample size; 14: Description of subjects.

1. *Strong evidence*: provided by generally consistent findings in multiple high quality RCTs.
2. *Moderate evidence*: provided by generally consistent findings in one high quality RCT and one or more low quality RCTs or by generally consistent findings in multiple low quality RCTs.
3. (A) *Limited evidence*: only one RCT (either high or low quality). (B) *Conflicting evidence*: inconsistent findings in multiple RCTs.
4. *No evidence*: no RCTs.

Generally, consistent findings were defined as 75% or more of the studies having statistically significant findings in the same direction.

3.3. Results

3.3.1. Study selection

The search resulted in 66 references via PsycINFO, 90 references in MEDLINE, 24 in EMBASE and 2 in CINAHL. After consulting the additional databases, Biological Abstracts, ERIC, LISA, OSH, Periodical Abstracts, SERFILE and Sociological Abstracts, the search yielded 97 different references. After deleting duplicates from all the databases consulted, the search finally resulted in 167 different references.

The first selection was based on titles, keywords and abstracts, and resulted in both reviewers selecting 26 empirical CRA studies and rejecting 141 studies. Of the rejected studies, 83 were non-CRA and 49 discussed and reviewed CRA but were not RCTs.

Furthermore, another five empirical studies (e.g. Meyers et al., 1998) reported on Community Reinforcement and Family Training (CRAFT) or interventions aimed at the involvement of family members (e.g. Sisson & Azrin, 1986) and an additional four were CRAFT reviews (e.g. Meyers, Miller & Smith, 2001). CRAFT, which is related to CRA, was developed on the basis of the belief that family members can make contributions in helping to persuade resistant substance

abusers to seek treatment (Meyers, Miller & Smith, 2001). Many skill-training strategies used in CRAFT are similar to those used in CRA, but are mainly focused on family members. It was therefore decided that CRAFT studies were not within the scope of this review.

Three additional studies were identified through reference checking (Azrin et al., 1994, 1996; Mallams et al., 1982). After reading the full papers, six of the selected 29 CRA studies were excluded because they were not RCTs.

One study (Mallams et al., 1982) was excluded because it did not evaluate a CRA program as defined by the inclusion criteria, and the intervention consisted of one component only ("Social club").

Another study (Schottenfeld et al., 2000) that was excluded investigated the number of alternative activities as main research objective in a population with an opiate as well as a cocaine addiction.

A CRA study to reduce AIDS risk behavior in an opioid-dependent population (Abbott et al., 1998a) did not focus on one of the outcome measures of interest, and was therefore excluded.

One study of sociopathic alcoholics was excluded because it investigated drinking outcomes in three treatment arms: (1) CRA, (2) individually focused cognitive behavioral treatment and (3) usual care (Kalman et al., 2000). However, no data on subjects receiving usual care were available (Kalman, 2002).

The study carried out by Abbott et al. (1999) was excluded because the data set, which was based on Abbott et al. (1998b), compared subjects who had entered a program with or without methadone as transfers from other community methadone programs.

Two studies carried out by Azrin et al. (1994, 1996) included subjects with different diagnoses of psychoactive substances, so they were excluded.

Two studies (Higgins et al., 1995; 2000b) were follow-up studies of previously published research (Higgins et al., 1993; 1994; 2000a), and Higgins et al. (1997) is a reprint of Higgins et al. (1995).

Four studies reported on the same two alcohol trials (Miller et al., 1992; Miller et al., 2001a,b) and homeless people (Smith et al., 1998; Smith & Delaney, 2001). Miller et al. (2001a,b), consisted of two complementary chapters (two search hits)

and is therefore considered as one trial in this review. Finally, a total of 11 trials were included (see Tables 3.1 and 3.2).

3.3.2. Methodological quality

The final results of the methodological quality assessment are presented in Table 3.1. For the critical appraisal of each individual study, 11 internal and 10 external validity criteria were assessed. The percentage of agreement, to assign a positive score, between the two reviewers (HGR and JJB) was 88 % for the internal validity criteria and 94 % for the external validity criteria. Subsequently, all authors were consulted to check this assessment and to provide relevant information. Three authors responded to the request and provided additional information on 8 studies. As a result, 23 of the "unclear" scores were changed to “positive”. The additional information from the authors also resulted in 25 of the “negative” scores being changed to “positive”.

In general, the methodological quality of the studies included in this review was high (see Table 3.1). Ten studies had 6 (> 50%) or more positive scores on the internal validity criteria, which was the pre-determined threshold for high quality (Abbott et al., 1998b; Azrin, 1976; Azrin et al., 1982; Bickel et al., 1997; Higgins et al., 1993, 1994, 2000a; Hunt & Azrin, 1973; Miller et al., 2001a,b; Smith et al., 1998).

Most of the studies did not include a blinded observer (item 5), and it was often unclear whether or not the researcher who performed the treatment allocation was aware of the treatment to which the subject was allocated (item 1b). With regard to the external validity criteria, several studies did not provide the CRA intervention according to a protocol (item 12d) and did not determine the adherence through tape/video-recording (item 12c). Many studies also had a small sample size (item 13).

3.3.3. Data extraction and study characteristics

Characteristics of the identified studies that were included (n = 11) are shown in Table 3.2. Five studies dealt with CRA in alcohol treatment (Azrin, 1976; Azrin et al., 1982; Hunt & Azrin, 1973; Miller et al., 2001a,b; Smith et al., 1998). The first two studies, which were the seminal studies for the entire CRA treatment, were inpatient studies and compared CRA versus usual care based on Jellinek (1960). Azrin's study (1976) added a disulfiram compliance-enhancing program to CRA. The first outpatient study (Azrin et al., 1982) compared CRA consisting of behavioral therapy plus a disulfiram assurance program with a disulfiram assurance program and disulfiram alone. The alcohol study carried out by Miller et al. (2001a,b) included two sub-groups: (1) disulfiram-eligible and (2) disulfiram-ineligible clients. The subjects were randomized to six-subgroups. Comparisons were made between usual care (with disulfiram) and (single) CRA (with disulfiram). Finally, one alcohol study dealt with a special population of homeless alcohol-dependent subjects (Smith et al., 1998). In this study, subjects were allocated to various conditions, such as eligible and ineligible for disulfiram. However, this study is based on a simplified two-condition collapsed design with the primary focus on comparing CRA with usual care. A minority of the CRA subjects was assigned to a disulfiram condition, so the CRA condition was considered to be single.

Four studies (Higgins et al., 1991, 1993, 1994, and 2000a) examined the effects of CRA with abstinence-contingent 'incentives' in the treatment of cocaine. In two studies (Higgins et al., 1991, 1993) the control group received "12-step counseling" as usual care, which is based on the disease model that is commonly used by community substance abuse clinicians in the U.S. One study compared CRA versus CRA with abstinence-contingent 'incentives' (Higgins et al., 1994), and one study (Higgins et al., 2000a) compared elaborate CRA, with abstinence-contingent incentives as an experimental condition, with non-contingent incentives.

Table 3.2. *Study characteristics of included studies*.

Population							Interventions			Results	
		CRA	Control	CRA	Control		CRA	Control			
Study	*Addiction*	*Mean age (year)*	*Mean age (year)*	*ASI composite scores* (range)	*ASI composite scores* (range)	*N*	*Freq. + duration*	*Freq. + duration*	*Interventions*	*Abstinence*	*ASI scores / percentage of drinking days / time spent drinking:*
Abbott, 1998b	Opioid	37.0		0.08 - 0.70	0.05 -0.66	180*	week 1-2 2/week. week 3-24 1/week	week 1-2 2/week. week 3-24 1/week	1) usual care (n=67) 2) CRA (n=52) 3) CRA + RP (n=62) Note: group 2&3 combined in analysis.	CRA groups (89%) vs. standard (78%), 3 consecutive weeks free from opiates $\chi 2 = 4.07$ d.f. = 1, P = 0.044	6-month ASI drug composite score in CRA groups vs. standard in favour of CRA; F=4.37, d.f.=1, 147, P = 0.038
Azrin, 1976	Alc.	XXX		XXX	XXX	18	30 h (1800 min.)	XXX	1) usual care + disulfiram (n=9) 2)CRA + disulfiram (n=9)	XXX	Percent of time spent drinking: ---> 16 weeks ≤ 24 weeks: 2% (2) vs. 55% (1), P < 0.005; after 2 years Follow-up in CRA condition, at least 90% abstain from drinking
Azrin, 1982	Alc.	33.9		XXX	XXX	43	1/week Mean 6.4 sessions	1 Control 1/week 4,9 sessions 2 Control 1/ week 4,5 sessions	1) usual care + disulfiram (n=14) 2) disulfiram compliance program (n=15) 3) single CRA + disulfiram (n=14)	XXX	Number of drinking days/ month: ---> 16 weeks ≤ 24 weeks: 0.9 (3) vs. 16,4 (1) vs. 7,9 (2), P < 0.001
Bickel, 1997	Opioid	33.6	34.6	0.14 – 0.56	0.18 – 0.56	39	3/week 60 min. 26 weeks	1/week 37 min 26 weeks	1) usual care (n=20) 2) CRA + abstinence contingent 'incentives' (n=19)	≤ 4 weeks: 55% (1) vs. 68% (2), ns; > 4 weeks ≤ 16 weeks: 5% (1) vs. 26% (2), $\chi 2$ (1, N=39)= 3.4, P = 0.06; > 16 weeks ≤ 24 weeks: 0% (1) vs. 11% (2), ns.	XXX
Higgins, 1991	Cocaine	29.0	30.5	0.21 -0.57	0.21 -0.46	25	2/week 60 min. 12 weeks	2/week 60 min. 12 weeks	1) CRA (n=13) 2) usual care (n=12)	≤ 4 weeks: 77% (1) vs. 25% (2); > 4 weeks ≤ 16 weeks: 46% (1) vs. 0% (2); period 1-12 weeks: $\chi 2 = 10.9$, d.f.= 1 , P = 0.001	XXX

		Population					Interventions			Results	
		CRA	Control	CRA	Control		CRA	Control			
Study	Addiction	Mean age (year)	Mean age (year)	ASI composite scores (range)	ASI composite scores (range)	**N**	Freq. + duration	Freq. + duration	Intervention	Abstinence	ASI scores / percentage of drinking days / time spent drinking:
Higgins, 1993, 95, 97, 2000b	Cocaine	28.5	30.1	0.19 - 0.59	0.17 - 0.49	38	1-12 weeks 2/week 60 min. 12-24 weeks 1/week 60 min.	1-12 weeks 2/week 210 min. 12-24 weeks 1/week 150 min or 1/week 60 min.	1) CRA + 'incentives' (n=19) 2) usual care (n=19)	≤ 4 weeks: 74% (1) vs. 16% (2); > 4 weeks ≤ 16 weeks: 68% (1) vs. 11% (2); > 16 weeks ≤ 24 weeks: 42% (1) vs. 5% (2), period 3-24 weeks: $\chi 2 = 7.84$, d.f.=1, P= 0 .005; 1 year: 96% (1) vs. 69% (2), $\chi 2$ (1, N= 38) = 7.3, P= 0.007	6 month composite ASI drug, alcohol, family-social and psychiatric scores improved compared to intake.
Higgins, 1994, 95,97, 2000b	Cocaine	31.8	30.9	0.11 - 0.54	0.12 - 0.65	40	1-12 weeks 2/week 60 min. 12-24 weeks 1/week 60 min.	1-12 weeks 2/week 60 min. 12-24 weeks 1/week 60 min.	1) CRA (n=20) 2) CRA + 'incentives' (n=20)	≤ 4 weeks; 75% (2) vs. 55% (1); > 4 weeks ≤ 16 weeks: 55% (2) vs. 25% (1); > 16 weeks ≤ 24 weeks: 30% (2) vs. 5% (1); period 1-24 weeks: $\chi 2$ (1) = 4.4, P= 0.03; 1 year: 13 (20) vs. 12 (20) ns	6 month composite ASI drug, alcohol, family-social and psychiatric scores improved compared to intake.
Higgins, 2000a,b	Cocaine	30.8	30.0	0.17 -0.49	0.12 - 0.53	70	1-12 weeks 2/week75 min. 12-24wk 1/week75 min. 24 weeks	1-12 weeks 2/week75 min. 12-24wk 1/week75 min. 24 weeks	1) CRA + 'incentives' (independent of urine sample) (n=34) 2) CRA + 'incentives' contingent on abstinence (n=36)	> 4 weeks ≤ 16 weeks: 45% (2) vs. 30% (1); $\chi 2$ (1, N=70) = 1,69, P = 0.19; > 16 weeks ≤ 24 weeks: 20% (2) vs. 10% (1); $\chi 2$ (1, N=70) = 1,60, P = 0.20	6 month composite ASI drug, alcohol, family-social and psychiatric scores improved compared to intake.
Hunt, 1973	Alc.	39.9	36.8	XXX	XXX	16	50 h (3000 min.)	25 h (1500 min	1) usual care (n=8) 2) single CRA (n=8)	XXX	Percent of time spent drinking: ---≤ 4 weeks: 14% (2) vs. 79% (1), P < 0.005; > 16 weeks ≤ 24: 20% (2) vs. 80% (1), P < 0.005

Population							Interventions			Results	
		CRA	Control	CRA	Control		CRA	Control			
Study	Addiction	Mean age (year)	Mean age (year)	ASI composite scores (range)	ASI composite scores (range)	**N**	Freq. + duration	Freq. + duration	Intervention	Abstinence	ASI scores / percentage of drinking days / time spent drinking:
Miller, 2001a,b	Alc.	31.0		XXX	XXX	237	Mean Group 3: 9.0 Group 4: 9.6 Group 6: 8.7 sessions	Mean Group 1: 9.5 Group 2: 7.9 Group 5: 7.3 sessions	1) usual care (n=39) 2) usual care + disulfiram (n=40) 3) CRA + disulfiram (n=40) 4) CRA (n=38) 5) usual care (n=41**) 6) CRA (n=39**) Note: 1-4 disulfiram-eligible subjects 5-6 disulfiram-ineligible subjects	> 4 weeks ≤ 24 weeks 1) 41.9% 2) 58.8% 3) 34.4% 4) 32.3% 5) 24.0% 6) 22.2%	> 4 weeks ≤ 24 weeks; Mean drinking days/week: 1) 1.35 2) 0.25 3) 0.20 4) 0.22 5) 1.69 6) 1.68
Smith, 1998	Alc.	38.0		XXX	XXX	106	Mean 39.3 group, 4.6 individual and 3.3 job club sessions	Mean 18.7 AA meetings and 0.8 sessions coun-seling	1) usual care (+ disulfiram) (n=42) 2) CRA (+ disulfiram) (n=64)	> 4 weeks ≤ 16 weeks: $\chi 2(1,N=95) = 10.614$, P = 0.001; > 16 weeks ≤ 24 weeks: $\chi 2(1,N=88) = 8.47$, P = 0.004	Number of drinking days/week ---> 4 weeks ≤ 16 weeks: F(1,88) = 1.56, P = 0.2145; > 16 weeks ≤ 24 weeks: F(1,77) = 8.35, P = 0.005; 1 year: F(1,70) = 3.32, P = 0.0771

*Note: The distributions of the ASI composite scores are reflected in two digits ranging from the lowest- to the highest score as mentioned in the study. The studies of Higgins (1995, 1997 and 2000(b) are not mentioned apart, because these studies contain follow-up assessments. The study of Abbott (1998b) included 180 subjects but used 151, who engaged in treatment, for analysis at 6 months of follow-up as is indicated by *. All studies were outpatient except Hunt & Azrin (1973) and Azrin (1976), which were inpatient. The sample distribution of the alcohol study of Miller (2001a,b) was calculated with data derived from the intention-to-treat sample and percentage of clients attending three or more therapy sessions and is indicated by **.*

Furthermore, two opioid studies were identified. One (Bickel et al., 1997) evaluated the effect of a 160-day buprenorphine dose-taper combined with either usual care or a behavioral treatment based on CRA with 'incentives'. The other study (Abbott et al., 1998b) compared the effects of CRA and usual care in a methadone maintenance program.

Three early studies reported their results in such a way that it was not possible to include them in the statistical pooling with respect to continuous variables, because they only provided means and no standard deviations (Azrin, 1976; Azrin et al., 1982; Hunt & Azrin, 1973). Data pertaining to time to relapse was not provided by the included studies, so no further considerations could be made.

3.3.4. Effectiveness of CRA in alcohol treatment aimed at abstinence

Single CRA versus usual care

Three high quality studies that were identified compared single CRA with usual care without disulfiram (Hunt and Azrin, 1973; Miller et al., 2001a,b; Smith et al., 1998).

The first study, which is the first CRA study, showed the effectiveness of CRA in treating alcohol-dependence in an in-patient setting, focusing on several aspects of life such as employment and time spent away from home (Hunt and Azrin 1973). At 6 months follow-up the CRA group showed a significantly lower percentage of 'time drinking' than the usual care group (14% versus 79%; $P < 0.005$). One limitation concerns the CRA treatment package. The early version(s) of CRA had technically fewer components available, and gradual decreased the number of counseling hours. Despite this, the number of treatment sessions of more recent CRA studies might depend on the type (severity) of target population being treated.

In the out-patient study carried out by Miller et al. (2001a,b) no difference was found between single CRA (22.2%) and usual care (24.0%) with regard to abstinence during 1-6 months and 16-24 months follow-up periods in subjects who were disulfiram-ineligible. The same was found with regard to the number of drinking days per week. There was also no statistically significant difference in

abstinence between the usual care group and the CRA group in disulfiram-eligible subjects (41.9% versus 32.3%). However, the CRA group performed much better, than the usual care group, with regard to the number of drinking days per week (0.22 versus 1.35).

A critical statement must be made concerning the 'contamination' of the research groups; 51.3 % of the subjects in the usual care group and 18.4 % of the subjects in the CRA group accepted disulfiram, despite ascertainment of the treatment condition. Subjects in the usual care group were encouraged to take disulfiram, in contrast to subjects in the CRA group.

In the third high quality RCT involving homeless alcoholics (Smith et al., 1998), participants in the CRA program had statistically significantly higher continuous abstinence rates, ranging from 2 months to 1 year after intake [at 8 weeks: ($\chi^2(1) = 10.61$, P = 0.001; at 16 weeks: $\chi^2(1) = 8.47$, P = 0.004; at 36 weeks: $\chi^2(1) = 7.16$, P = 0.01)]. The same significant findings applied to the number of drinking days. However, some critical comments should be made: the study included a specific population, and only a minority of the subjects (disulfiram eligible and motivated to comply) took disulfiram. In the analyses, the subgroups were combined and in this review they are considered to have received no disulfiram.

The number of drinking days (continuous variable) reported by Miller et al. (2001a,b) and Smith et al. (1998) were merged into a meta-analysis. The data from the proximal follow-up (Miller et al., 2001a,b) and the 6-month follow-up data (Smith et al., 1998) were considered as long-term effects (16 < weeks ≤ 24). Using the random effects model, the number of drinking days was [WMD (95% CI) = -0.94 (-1.60 to –0.27, Q=2.75, d*f* 2)] in favor of CRA. With respect to this statistical pooling, the potential source of heterogeneity regarding the follow-up, population and disulfiram eligibility affects the interpretation of this robust finding and should be considered with caution.

Overall, there is strong evidence (level 1) that single CRA is more effective than usual care with regard to number of drinking days, and there is conflicting evidence (level 3) with regard to continuous abstinence.

CRA with disulfiram versus usual care with disulfiram

Three of the studies that were included (Azrin, 1976; Azrin et al., 1982; Miller et al., 2001a,b) compared CRA with disulfiram versus usual care with disulfiram. The in-patient study carried out by Azrin (1976), which was of high quality, showed significant results at 6 months follow-up in favor of CRA with disulfiram in terms of time drinking (2% versus 55%, $P < 0.005$), employment, time spent away from home and time institutionalized. These benefits were maintained for at least 2 years following discharge from the hospital.

The high quality study carried out by Azrin et al. (1982), which included three treatment conditions, also compared CRA with disulfiram versus usual care with disulfiram. At 6 months follow-up, the percentage of time drinking was significantly lower in the CRA with disulfiram group than in the control group (3% versus 55%, $P < 0.01$). The CRA with disulfiram group also showed a statistically significant difference with regard to amount of alcohol consumed and ethanol intoxicated moments.

A limitation concerns the acceptance of disulfiram. In the group receiving usual care, based on Jellinek (1960), disulfiram use was encouraged. However, compliance in the usual care and in the disulfiram condition was extremely poor (Azrin et al., 1982): the mean number of days of disulfiram consumption was 0 in the usual care with disulfiram group versus 24.8 in the CRA with disulfiram group ($P < 0.001$). The total CRA therapy program was reduced from an average of 30 h (Azrin, 1976) to 6.4 h (Azrin et al., 1982), which also complicates comparison of the two studies.

In a high quality study, Miller et al. (2001a,b) found some evidence in favor of usual care: 58.8% of the subjects receiving usual care with disulfiram, were still abstinent at 1-6 months of follow-up, compared to only 34.4 % in the CRA with disulfiram group. This result was not statistically significant. At long-term follow-up (16-24 months) this difference had dissipated. There was also no statistically significant difference in drinking days per week (0.20 in the CRA group versus 0.25 in the usual care group). A critical comment can be made with respect to treatment integrity. The usual care with disulfiram used a compliance procedure (Sisson & Azrin, 1986), which can also be regarded as a part of a CRA-program.

This may have reduced the contrast. In the usual care group, 90 % of the subjects accepted disulfiram, and over 80% were rated by the therapist as compliant. In the CRA with disulfiram group 56.4% accepted disulfiram and 44.1% were compliant. All subjects treated in these two groups were disulfiram-eligible. The study carried out by Miller et al. (2001a,b) also shows that when data is combined during follow-up (1-6 months), the subjects in the disulfiram-eligible group, who received CRA were drinking on significantly fewer days (3% versus 19%, $P < 0.001$) than the subjects in the usual care group.

In summary, there is moderate evidence (level 2) that CRA with disulfiram is more effective than usual care with disulfiram in terms of number of drinking days, and limited evidence (level 3) that there is no difference in effect between CRA with disulfiram and usual care with disulfiram in terms of continuous abstinence.

3.3.5. Effectiveness of CRA in cocaine treatment aimed at abstinence

Single CRA versus usual care

No RCTs were identified that examined the effects between single CRA and usual care, so there is no evidence (level 4).

CRA with abstinence-contingent' incentives' versus usual care

A meta-analysis was conducted on two studies (Higgins et al., 1991, 1993), the latter of which was of high quality, to determine the effect of CRA with 'incentives' versus usual care (details are presented in Table 3.2). Using the random effects model, the pooled relative risk for cocaine abstinence in a CRA treatment program with a duration of 4 weeks or less was 3.75 [(95% CI) 1.79 to 7.87, Q = 0.31, d*f* 1], and for a CRA treatment program with a duration between 4 and 16 weeks it was 5.09 [(95% CI) 1.63 to 15.86, Q = 0.44, d*f* 1].

There is strong evidence (level 1) that CRA with 'incentives' is more effective with regard to cocaine abstinence than usual care.

CRA with abstinence-contingent 'incentives' versus CRA (non-contingent incentives)

Two studies (Higgins et al., 1994, 2000a), both high quality RCTs, determined the effect of CRA with abstinence-contingent 'incentives' versus CRA (non-contingent incentives). Higgins et al. (1994) examined the difference between CRA versus CRA with abstinence-contingent 'incentives', and Higgins et al., (2000a) compared CRA both with and without abstinence-contingent 'incentives'. In the latter study all patients received CRA and the experimental condition depended on whether it was combined with cocaine abstinence-contingent vouchers or vouchers provided independent of cocaine use (details are presented in Table 3.2). For the purpose of statistical pooling, the CRA with non-contingent 'incentives', which attenuates clinical homogeneity, was considered to be single CRA. The results of this pooling were calculated for an intermediate term, as no short-term data were available. The pooled effect size for cocaine abstinence in a CRA treatment program with duration of 4-16 weeks was 1.73 [(95% CI) 1.04 to 2.88, Q = 0.48, d*f* 1].

There is strong evidence (level 1) that CRA with abstinence-contingent 'incentives' is more effective than single CRA (non-contingent incentives) treatment aimed at cocaine abstinence.

3.3.6. Effectiveness of CRA in opioid treatment aimed at abstinence

CRA with 'incentives' versus usual care in a detoxification program

One identified RCT (Bickel et *al*., 1997) compared a 160-day buprenorphine dose-taper combined with either usual care or a behavioral treatment based on CRA with 'incentives'. Fifty-three percent of the subjects receiving CRA with 'incentives' completed the treatment, versus 20% receiving usual care [χ^2 (1, N = 39) = 4.5, P = 0.03]. In the short-term (≤4 weeks) the CRA with 'incentives' was more effective (68%) in terms of continuous abstinence than usual care (55%), but this was not statistically significant. In the intermediate term, more participants in the CRA with 'incentives' (47%) achieved at least 8 weeks of continuous abstinence [χ^2 (1, N = 39) = 4.8, P = 0.03], compared to usual care (15%). In the

long term (> 16 and ≤ 24 weeks) there was still a difference (11% versus 0%), but this was not statistically significant.

Hence, there is limited evidence (level 3) that CRA with 'incentives' is more effective than usual care in a detoxification program.

CRA with 'incentives' versus single CRA in a detoxification program

No RCTs were identified that examined the effects of CRA with 'incentives', either separately or versus usual care, so there is no evidence (level 4).

CRA versus usual care in a relapse prevention program

No RCTs could be identified, so there is no evidence (level 4).

Single CRA versus usual care in a methadone maintenance program

One RCT (Abbott et al., 1998b) was identified, with three treatment arms: usual care, CRA, and CRA with relapse prevention (CRA/RP). We considered methadone maintenance to substitute and prevent illegal drug use. In the long term (> 16 weeks) CRA was significantly more effective than the usual care, based on the consecutive (3 weeks) opiate-negative urine analysis (84% versus 78%) and the 6-month ASI composite scores. However, there might be some limitations in this study. Firstly, with regard to the design: combining treatment arms 2 (CRA) and 3 (CRA with relapse prevention). Nevertheless, by the time of 6-month follow-up the mean number of RP sessions was 1.06. When this number is contrasted with the attended 20 CRA sessions, one could say that these conditions are essentially the same and legitimatize collapsing. Secondly, in the follow-up: 29% of the urine samples were missing.

Hence, there is limited evidence (level 3) that single CRA is more effective than usual care in a methadone maintenance program.

3.4. Discussion

3.4.1. Clinical implications

In general, there is limited to moderate evidence for the efficacy of CRA with or without medication or contingency management in various substance-related disorders, including alcohol, cocaine and heroin. It can be argued that the collapsing of alcohol, cocaine and opioid findings might cause a misinterpretation of this meta analysis. For instance, the voucher approach is often used in the CRA drug treatment (via dichotomous variable) and is, in general, absent in the alcohol treatment. Also the support for the effectiveness on CRA with alcohol abusers is rather bit stronger than for the drug populations. Additionally, the reported findings vary substantially depending on the type of variable are reviewed (e.g. alcohol outcomes with respect to dichotomous and continuous variables).

On the other hand the combining of the meta-analysis' findings seems legitimate, because one could ask why to distinguish studies on the basis of the drug of dependence? CRA addresses the behavior of addiction; not the physiological basis derived from the drug that is being used. It seems viable that the focus on the outcome of abstinence is comparable across various substance types (Gowing, 2003).

Due to the course of the progression of addiction, which is similar to that of chronic diseases (O'Brien, 2003), there is a cumulating of evidence to view addiction as a chronic, relapsing brain disease (Leshner, 1997; McLellan, 2002; Van den Brink et al., 2003). In general, this view has generated a variety of treatment goals, such as crisis intervention, stable abstinence, stabilization of substance use and improving quality of life (harm-minimization) and palliation (Van den Brink et al., 2003). These different treatment goals determine the type of defined outcome measures, which in turn, correspond with the different treatment goals such as abstinence (e.g. Azrin, 1976; Higgins et al., 1993) and harm-minimization (e.g. Abbott et al., 1998a). This view of chronic disease legitimizes a

focus on the choice of continuous outcome variables rather than dichotomous variables. Although we defined outcome measures such as addiction severity, frequency of substance abuse and time to relapse, data was often not provided. In addition, analogue to these treatment goals, the use of a pharmacological agent such as disulfiram is solely associated with abstinence in the treatment of alcohol abuse and renders also the goal of a concomitant psychosocial therapy such as CRA. Nevertheless, with respect to the palette of treatment goals the choice to focus on abstinence can be argued. The more sensitive nature of continuous measures might provide a better outcome perspective for CRA. But abstinence is the outcome measure that is most easily assessed objectively and hence becomes the obvious primary outcome indicator, as identified in the methods section (Gowing, 2003).

Currently, there are 3 dominant researchers conducting studies in the CRA area: Nathan Azrin, Stephen Higgins and Robert Meyers. In nearly all included studies Azrin, Meyers and Higgins are directly involved as (co) authors.

Most of the included studies were of high methodological quality. Only a few studies could be identified within each type of comparison, i.e. CRA versus usual care and CRA versus CRA with contingency management for alcohol, cocaine and opioid abuse.

With respect to the alcohol studies, it was demonstrated that there is limited evidence (level 3) that single CRA with or without disulfiram is more effective, in terms of continuous abstinence, than usual care. However, there is moderate evidence (level 2) that single CRA with or without disulfiram is more effective than usual care in terms of number of drinking days. Furthermore, these results that favor CRA support the findings that CRA is also effective in the treatment of alcohol abuse in specific populations, some of which have severe life-problems, such as homeless (Smith et al., 1998; Smith & Delaney, 2001). Other specific populations have also been the subject of research on CRA: Dine' (Navajo) people (Miller et al., 1999b) and sociopathic alcoholics (Kalman et al., 2000).

It is noteworthy that significantly more disulfiram-eligible clients than disulfiram ineligible subjects were completely abstinent during 1-6 months of follow-up (Miller et al., 2001a,b). However, as previous noted, the treatment integrity of

Miller (2001a,b) study was affected, because the usual care condition with disulfiram used a CRA compliance procedure (Sisson & Azrin, 1986). From its inception, it seems important to advocate procedures in CRA (i.e. via significant others) to increase acceptance and compliance with the medication regime (e.g. Sisson & Azrin, 1986). An important finding was the interaction between effectiveness of disulfiram-compliance procedure and marital status of the subjects [$F(2,41) = 6.12$, $P < 0.006$]. For married subjects who participated in the full CRA program, the therapy outcome showed no improvement (Azrin et al., 1982).

Higgins and his co-workers investigated two operant-oriented programs for the treatment of cocaine dependence: community reinforcement and contingency management via 'incentives'. There is strong evidence that the combination package (CRA with contingency management) is superior to usual care (level 1) or CRA with non-contingent 'incentives' (level 1). In every study, CRA with abstinence-contingent 'incentives' is significantly more effective than usual care in cocaine-dependent subjects.

However, the fact that this treatment package consists of two combined operant-oriented methods is a limitation. These cocaine studies do not address single CRA, so there is no evidence that single CRA is more favorable than usual care. A recent RCT demonstrated that there is no evidence that CRA produces larger effect sizes than vouchers in cocaine abusers. Nevertheless, with regard to alcohol use, employment, and other outcomes, CRA produced greater effects than vouchers (Higgins et al., 2003).

Furthermore, on base of urinalyses, it seems clear that the effect of incentives, as a part of a larger CRA intervention, dissipates slowly after discontinuation. The collapsing of the data provided by Higgins et al. (1994, 2000a) should be interpreted with caution. In a certain degree the collapsing seems understandable, however, we don't know how it affected other variables; the clients experience. Another critical comment that can be made regarding external validity concerns the relatively low ASI composite scores. This is possibly associated with the enrolment of the participants, who were mainly recruited through advertisements in newspapers and via public service announcements on

different media channels. This might affect the generalizability of the results to different study populations. In general, the severity of the symptoms worsens the prognoses (McLellan et al., 1983). Furthermore, it should be noted that the same research team conducted all the RCTs that were identified.

The literature search revealed that small naturalistic studies have also been conducted to assess the efficacy of CRA with contingent management in cocaine and marijuana abuse (Budney et al., 1991; Vick and Houden, 1991), and even in an individual with a dual diagnosis (Fix, 2001). A larger study has also been conducted to examine the power of CRA in a population with mainly cocaine and marijuana abuse (Azrin et al., 1994). This study demonstrated that CRA, even when a worst-case analysis was conducted, was superior to supportive counseling in reducing the mean number of days of drug use at the end of 8 months of treatment (49.1% versus 78.3%, $P < 0.003$) and the effect sustained after 9 months of follow-up (52.8 versus 80.4%, $P < 0.004$; Azrin et al., 1996). Urine analysis supported this outcome in the last month of treatment [$\chi^2(1) = 6.05$, $P = 0.014$). At follow-up there was a statistically non-significant trend in favor of CRA [$\chi^2(1) = 3.38$, $P < 0.066$].

There were no RCTs that determined the effect of single CRA in an opioid detoxification or a relapse prevention program to treat opioid dependency. Nevertheless, one naturalistic study that was identified examined the role of CRA during a rapid opioid detoxification process and, additionally, CRA in a naltrexone maintenance program aimed at abstinence, which showed promising results (Roozen et al., 2003).

Hence, with respect to the CRA programs focussing on opioid substitution (Abbott et al., 1998b), detoxification (Bickel et al., 1997) and abstinence (Roozen et al., 2003), it seems that, there is limited evidence and optimistic and promising research findings. Abbott et al. (1998a) examined the role of CRA in risk-behavior, including injection drug use and high-risk sexual behavior, to prevent AIDS. These types of behavior were significantly, although comparably reduced in all treatment groups (Higgins & Abbott, 2001). In the treatment of opioid dependence, CRA could be an option to realize further optimization of the treatment outcome.

Based on the results of a variety of cocaine and opioid studies it becomes clear that abstinence-contingent incentives are an effective approach. This reinforcement principle is also a basic premise of CRA, and is supported by Azrin et al. (1996) who stated: "the favorable results appear attributable to the inclusion of a significant other in therapy and the use of reinforcement abstinence contingent 'incentives'". Problems might be encountered in the implementation of abstinence-contingent incentives in clinical routine practice, but pertaining to the token economy, there might be options that could make this approach feasible (cf. Franco et al., 1995).

CRA is associated with relatively intensive and time-consuming treatment (Barber, 1992). The initial study (Hunt & Azrin, 1973) took an average CRA time of 50 h. This was reduced to 30 h in the next study (Azrin, 1976) and was completed in approximately 6 h in the Azrin study in 1982. These data suggest that claims about the high treatment and labor intensity can be refuted. It has recently been demonstrated that CRA treatment can improve many aspects of life in approximately 5 sessions over a period of in 4-6 weeks. Subsequently, the CRA treatment can be tailored and adapted to individual goals, varying from life-long abstinence to moderation of substance use (Miller, 2001c).

As previously discussed, a limitation of this review is the absence of dependent measures such as the amount of alcohol consumed, blood alcohol concentrations or the number of non-drug related activities. The inclusion of such continuous measures might be considered as direct measures of the effectiveness of CRA.

Another limitation concerning the conducted analyses is the elimination of the early CRA studies from the statistical pooling due to insufficient data available.

3.4.2. Research implications

Most studies included in this systematic review evaluated a cognitive behavioral 'treatment package'. A CRA manual for the treatment of alcohol abuse that has been published describes the appropriate CRA elements for clinical use (Meyers & Smith, 1995). A treatment manual is also available for the combined

approach in the treatment of cocaine dependence (CRA and vouchers, Budney & Higgins, 1998), which was used as a guideline in nearly all of the identified cocaine studies.

One limitation is that we know little about the actual or comparative value of the different elements within CRA. Although we have underlined some critical elements, it is still unclear which element within the CRA framework is the most effective, and which components of CRA are necessary and which are superfluous. A conceptual analysis appears to be necessary. This seems especially relevant now that the biopsychosocial model has been widely accepted and multidimensional approaches are gaining terrain in the treatment of addiction. Among the possible key elements of CRA that have been suggested is a CRA pharmacotherapy–compliance procedure (Sisson & Azrin, 1986), to encourage taking pharmacological agents under supervision in order to prevent omissions of medication intake and to increase adherence to treatment. This, in turn, results in a reduction in therapy time, thus reducing costs and increasing benefits (e.g. Azrin et al., 1982; Miller et al., 2001a,b). In several studies CRA outperformed other treatment modalities in terms of participation in non-drug-related activities (i.e. Higgins et al., 2003; Schottenfeld et al., 2000). The latter authors suggested that reinforcement of non-drug-related social, vocational, and recreational activities are a crucial component of CRA. This is also supported by Mallams et al. (1982), who suggested that a peer-group social reinforcement (i.e. community social club) should be arranged to improve therapy outcome. These non-substance-related reinforcement activities seem to be an important element of CRA to maintain a long-term substance-free lifestyle.

Future RCTs should aim at identification of the most effective components of CRA programs. In addition to maintaining high internal validity, efforts should be made to conduct RCTs with a high(er) external validity. Considerable attention should be paid to training therapists in the application of CRA, and making tape recordings or similar procedures to assess treatment integrity. It is therefore a prerequisite that CRA procedures are protocol-based. Additionally, a clear description of the control program (usual care) should also be given.

We recommend:

1. More high quality RCTs of CRA in the treatment of alcohol, cocaine and opioid addiction.
2. RCTs conducted by other research groups in different countries and/or different settings to confirm the most promising findings.
3. RCTs focusing on the severity of addiction.
4. RCTs with a larger sample size, which is determined by a power analysis.
5. RCTs including CRA treatments that are protocol-based and adherence determined through tape/video-recording.
6. More RCTs with a follow-up of one year or longer.
7. RCTs of CRA with and without 'incentives' with multiple follow-up measurements.

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Acknowledgements

We would like to thank Linda Gowing, PhD and Stephen Higgins, PhD for their comments on an earlier draft. We also thank Mario ter Smitten for his assistance in the search strategy.

CHAPTER 4

A systematic review of the effectiveness of naltrexone in the maintenance treatment of opioid and alcohol dependence

Abstract

This systematic review summarises evidence of the effectiveness of naltrexone (NTX) and the added value of psychosocial treatment in the maintenance treatment of opioid and alcohol dependence.

Studies were selected through a literature search, conducted in March 2004. Seven opioid and seventeen alcohol studies were identified. Where possible, meta- (regression) analyses were performed. There is lack of evidence about the effectiveness of NTX in the treatment of opioid dependence. There is evidence for the effectiveness and applicability of NTX in the management of alcohol dependence. The opioid studies combined NTX with a variety of psychosocial interventions, which plagued the evaluation of their value. Concomitant psychosocial interventions used in the alcohol studies were mainly cognitive behavioral, which seems to be more favourable than NTX combined with supportive therapy. In general, the auxiliary therapies fail to ameliorate dropout and NTX's non-compliance.

4.1. Introduction

Naltrexone (NTX), an opioid antagonist, blocks intrinsic properties of psychoactive substances that act on the μ, κ, and δ opioid receptor sites by competitive occupation. It is ascertained that alcohol acts on the opioid receptor sites. By blocking these sites, NTX prevents the reinforcing effects of alcohol consumption (O'Brien, Volpicelli & Volpicelli, 1996).

The metabolic pattern of NTX predominantly involves the reduction of NTX into 6-β-hydroxy naltrexone (6-β-naltrexol; Wall et al., 1981). The long acting properties of NTX are mainly due to this metabolite, which has an elimination half-life ($T_{1/2}$) of approximately 13 hours compared to the parent drug with a $T_{1/2}$ value of 4 hours. The dose-related antagonism on both subjective and objective responses has been subject to some research, although these findings are based on small samples (Resnick et al., 1974; Verebey, 1981). NTX and 6-β-naltrexol are dose proportional (linear increase) in terms of AUC and C_{max} over the range of 50 to 200 mg. A bio-equivalence was demonstrated after 100-mg single doses (Meyer et al., 1984). Despite the excellent pharmacological (blocking) properties, in practice NTX treatment is often hampered by dropout, non-compliance and consequently relapses into opioid or alcohol abuse (Rothenberg et al., 2003; Tucker et al., 2004).

In general, pharmacological interventions suffer from poor compliance (O'Brien and McLellan, 1996; Weiss, 2004). To promote adherence to NTX regimes and to initiate and maintain lifestyle changes, behavioral and psychosocial interventions have been developed (Miller & Wilbourne, 2002). However, evidence is scant regarding the question whether and which type of psychosocial intervention should be combined with NTX treatment in order to optimise its effectiveness.

Recently, several systematic reviews and meta-analyses have been published regarding the effectiveness of NTX in the treatment of alcohol dependence (Bouza et al., 2004; Fiellin et al., 2000; Garbutt et al., 1999; Kranzler & Van Kirk, 2001; Miller & Wilbourne, 2002; Sinclair, 2001; Srisurapanont & Jarusuraisin, 2004; Streeton & Wheelan, 2001; Swift, 1999). In general, these studies conclude that

NTX is more favourable in terms of abstinence, percentage of drinking days and the number of drinks than a placebo in the treatment of alcohol dependence.

In contrast to the alcohol literature, only a few reviews could be identified, which have assessed the effectiveness of NTX maintenance in opioid dependent participants (Kirchmayer et al., 2002; O'Connor & Fiellin, 2000; Van den Brink & Van Ree, 2003). These studies conclude that the evidence on the surplus value of NTX over placebo is minimal and conflicting at best.

First and foremost, the current study was conducted to unfold and update the effectiveness of NTX, because the previously mentioned reviews did not include several recent studies on NTX maintenance. To summarise the available (recent) evidence on the effectiveness of NTX, in the maintenance treatment of alcohol and opioid dependence, a systematic (meta-analytic) review was conducted with the following aims:

1. to study the effects of NTX compared to placebo in the maintenance treatment of opioid and alcohol dependence;
2. to study whether combining NTX with psychosocial treatment is more effective than treatment with NTX alone.

4.2. Experimental procedures

4.2.1. Criteria for considering studies for this review

Randomised (placebo) controlled trials (RCTs) and controlled clinical trials (CCTs) with NTX maintenance treatment were included. When group allocation in a trial was determined randomly, the study could be labelled as an RCT. If the randomisation procedure was unclear, but considered as randomised (e.g. double-blind study), the trial was assumed to be a CCT.

RCTs and CCTs had to include participants with alcohol or opiate abuse or dependence (DSM-III-R or DSM-IV) between 18 and 75 years of age. Only RCTs and CCTs in outpatient settings were included to diminish clinical heterogeneity. Specific populations (populations such as federal probationers, prisoners and healthcare professionals) were omitted as the outcomes may be biased. RCTs and

CCTs had to report data on at least one of the following outcome measures: (1) relapse rates, with relapse defined as drinking at least four alcoholic drinks for women, five for men on an occasion or single day; and (2) (continuous) abstinence, confirmed by urine samples, blood samples or self-reports. When data on continuous abstinence was not available, abstinence percentage (i.e. the proportion of participants abstinent during the follow-up period) was included; (3) frequency of substance abuse (percentage of drinking days or days using drugs); (4) time to first relapse and (5) time to first drink. It must be noted that relapse is the most sensitive outcome measure linked to the assumed mechanisms of NTX's action, which is the reduction of the reinforcing pleasure when drinking alcohol (Volpicelli, 1997; Littleton & Zieglgansberger, 2003) or when using opioids.

4.2.2. Search strategy for identification of studies

Relevant RCTs meeting the inclusion criteria were identified by:

1. A computer-aided search using the following databases: Pubmed, EMBASE, PsychINFO and the Cochrane Controlled Trials Register (CCTR). All databases were searched from the date of commencement. The search was conducted in March 2004, using the first two stages of the search strategy recommended in the Cochrane Handbook (Appendix V of Section V) and published by Alderson, Green and Higgins (2004). This strategy was run in conjunction with combinations of the following keywords: naltrexone, alcohol abuse, substance abuse, drug abuse, alcohol(-)related disorder(s), opioid(-)related disorder(s), opiate(-)related disorder(s), alcohol dependence and opioid dependence. Only RCTs that were published in the English language were included.
2. Reference checking of identified trials and reviews.

4.2.3. Methods of the review

Two reviewers, (RdW and HGR) independently assessed the methodological quality and extracted the data from the included trials. The criteria list for

experimental studies (RCTs and CCTs), issued by the Cochrane Drugs and Alcohol Group was used to assess the methodological quality (Ferri, 2003). The full criteria list with operationalisations is available on request from the corresponding author. The guidelines of the Cochrane Drug and Alcohol Group consider six criteria including randomisation (range 0-2), allocation concealment (range 0-6), blinding (range 0-3), inclusion of all patients in the analysis (range 0-3), similarity of baseline characteristics (range 0-1) and equal treatment of groups (range 0-1). A total score was computed by summing the scores of all six criteria (range 0-16). Low quality was defined by a 0-8 score, and high quality by 9 (> 50%) or higher.

Statistical pooling was performed for subsets of studies that were clinically sufficient homogeneous with respect to population, interventions and outcome assessment. Statistical heterogeneity was assessed by visually inspecting forest plots, and quantified with the Q-test (χ^2). Study results were considered heterogeneous when $P \leq .05$. Meta-analyses were performed for medium term (>4 and ≤16 weeks) and long term (>16 and ≤ 32 weeks) treatment effect (Van Tulder et al., 2003, adapted). Pooled Risks Differences (RD) were computed for dichotomous outcomes (relapse rate, abstinence) and Weighted Mean Differences (WMD) for continuous outcomes (percentage drinking days per time period, time to first relapse and time to first drink), along with 95% Confidence Intervals (CI) using the random effects model. For dichotomous outcomes the number needed to treat (NNT) was also computed.

A qualitative analysis was also performed using a four-level rating system for the strength of the scientific evidence (Van Tulder et al., 2000):

1. Strong evidence - provided by generally consistent findings in multiple high quality RCTs.
2. Moderate evidence - provided by generally consistent findings in one high quality RCT and one or more low quality RCTs or by generally consistent findings in multiple low quality RCTs.
3. A. Limited evidence - only one RCT (either high or low quality);
   B. Conflicting evidence - inconsistent findings in multiple RCTs.
4. No evidence - no RCTs.

Generally consistent findings were defined as 75% or more of the studies having statistically significant findings in the same direction.

Subgroup analyses were carried out to analyse the potential influence of the type of co-intervention on the efficacy of NTX: individual or group psychotherapy. Meta-regression analysis was used to determine the statistical significance of subgroup effects. Weighted and unweighted linear regression analyses were carried out using individual RCTs as the unit of analysis (dependent variable). The inverse of the variance ($1/SE^2$) was used to weigh effect estimates of individual RCTs. The type of co-intervention was introduced in the model as independent variable.

To estimate the effect of (non-)compliance on outcome we calculated, where possible, the magnitude of the linear relationship between effect size (RD for dichotomous outcomes and WMD for continuous outcomes) and treatment retention by Spearman's non-parametric correlation.

4.3. Results

4.3.1. Study selection: NTX in opioid studies

After consulting Pubmed, EMBASE, PsychINFO and CCTR 119, 275, 149 and 65 publications, including duplicates, were identified respectively. Only seven placebo-controlled trials on maintenance treatment of opioid dependence met the selection criteria and were included in the review (Brahen et al., 1977; Guo et al., 2001; Hollister et al., 1978; Lerner et al., 1992; Mello et al., 1981; San et al., 1991; Shufman et al., 1994).

4.3.2. Study selection: NTX in alcohol studies

The search via Pubmed, EMBASE, PsychINFO and CCTR yielded 136, 461, 101 and 165 publications, including duplicates, respectively. The first selection was based on titles, keywords and abstracts. Initially, 27 studies were selected.

After reading the full articles, three studies were excluded because the studies encompassed experiments such as cue reactivity assessment during the study (Monti et al., 1999; Monti et al., 2001; Rohsenow et al., 2000). One study did not report on at least one of the outcome measures of interest and was therefore excluded (Monterosso et al., 2001). Another study was excluded, because it used an inpatient treatment of 21 days (Knox & Donovan, 1999). A recent study by Oslin et al. (2003) used participants of three aggregated studies containing one included study (Kranzler et al., 2000), an excluded study (Monterosso et al., 2001) and unpublished data, and was left out. Furthermore, a study used a nested sequence of 3 randomised trials and was excluded because the first ten months were not placebo-controlled (O'Malley et al., 2003). Three studies were excluded because the studies reported data from an earlier published parent trial: Cramer et al., 2003 derived data from Krystal et al., 2001; Oslin et al., 2002 used data from Oslin et al., 1997a and Monterosso et al., 2001; Pettinati et al., 2000, used data from the study of Volpicelli et al., 1992.

Finally, a total of seventeen discrete placebo-controlled trials on alcohol dependence were included (Ahmadi & Ahmadi, 2002; Anton et al., 1999; Balldin et al., 2003, Chick et al., 2000; Gastpar et al., 2002; Guardia et al., 2002; Heinälä et al., 2001; Kiefer et al., 2003; Kranzler et al., 2000; Krystal et al., 2001; Latt et al., 2002; Lee et al., 2001; Morris et al., 2001; O'Malley et al., 1992; Oslin et al., 1997b; Volpicelli et al., 1992; Volpicelli et al., 1997). Furthermore, two follow-up studies were included, Anton et al., 2001, a follow-up study of Anton et al., 1999, and O'Malley et al., 1996, a follow-up study of O'Malley et al., 1992. Finally, the study of O'Malley et al., 1995 was also included, which used data from two trials (O'Malley et al., 1992, and Volpicelli et al., 1992).

4.3.3. Methodological quality

The results of the methodological quality assessment are presented in Table 4.1. The percentage of agreement between the two reviewers was 89.5 % (κ = .848, P < 0.0001) for the validity criteria. In general, the methodological quality of the studies included in this review was high; 21 out of the 24 trials were assigned scores of 9 points or higher (M = 9.74, SD = 1.63, range 7-13). The methodological quality of the alcohol studies was somewhat higher (M = 10.00, SD = 1.69) than the opioid studies (M = 9.00, SD = 1.29), but this difference was not statistically significant. Frequently encountered problems were a lack of (information about) concealment of the randomisation, and the fact that in many studies not all patients who were randomised were included in the (ITT) analysis.

4.3.4. Opioid studies: effectiveness of NTX

The seven studies on opioid dependence showed wide heterogeneity in population, intervention, and outcome assessment. Therefore statistical pooling was not legitimate. Four studies reported on abstinence rates verified by urinalysis (Guo et al., 2001, Lerner et al., 1992, San et al., 1991; Shufman et al., 1994).

On the medium term, two studies reported no statistically significant difference on abstinence between NTX and placebo (Lerner et al., 1992; San et al., 1991). Two other studies reported differences in abstinence rates in favour of NTX (Guo et al., 2001 and Shufman et al., 1994), but in only one trial this difference was statistically significant (Guo et al., 2001).

Long-term effects of NTX were only reported in two studies (Guo et al., 2001 and San et al., 1991). One study showed a statistically significant difference in favour of NTX regarding abstinence rates (Guo et al., 2001). One study reported no significant difference on the long term (San et al., 1991).

4.3.5. Opioid studies: compliance of NTX

There was no statistically significant or relevant relationship between the effect size, which was calculated for each included study and treatment retention over the studies.

Table 4.1. *Methodological quality assessment of seven studies in the treatment of opioid dependence and seventeen studies in the treatment of alcohol dependence.*

First author, year	1	2	3	4	5.1	5.2	Total
Opioid studies							
Brahen, 1977	1	3	3	0	0	1	8
Guo, 2001	2	3	3	0	1	1	10
Hollister,1998	1	3	3	0	0	0	7
Lerner, 1992	2	3	3	0	0	1	9
Mello, 1981	1	3	3	2	1	1	11
San, 1991	1	3	3	0	1	1	9
Shufman, 1994	1	3	3	0	1	1	9
Alcohol studies							
Ahmadi, 2002	1	3	3	0	1	1	9
Anton, 1999	2	3	3	2	1	1	12
Balldin, 2003	2	6	3	0	1	0	12
Chick, 2000	1	3	3	0	1	0	8
Gastpar, 2002	1	3	3	0	1	1	9
Guardia, 2002	1	3	3	3	1	1	12
Heinälä, 2001	1	3	3	2	1	0	10
Kiefer, 2003	2	6	3	0	1	1	13
Kranzler, 2000	1	3	3	0	1	1	9
Krystal, 2001	1	3	3	0	1	1	9
Latt, 2002	2	3	3	0	1	1	10
Lee, 2001	1	3	3	0	1	1	9
Morris, 2001	1	3	3	0	1	1	9
O'Malley, 1992	1	3	3	3	0	1	11
Oslin, 1997	1	3	3	0	1	1	9
Volpicelli, 1992	1	3	3	2	1	1	12
Volpicelli, 1997	2	6	3	0	1	1	13

Note: the following Cochrane quality criteria were defined: 1. Randomisation (score: 2,1 or 0); 2. Allocation concealment (score: 6,3 or 0); 3. Blinding (score: 3,1 or 0) 4. Inclusion of all patients in the analysis (score: 3,2 or 0) 5. Other criteria: 5.1 Similarity of the groups at the start of the trial (score: 1 or 0) 5.2, Groups were treated equally (aside from the experimental intervention (score: 1 or 0)). Two follow-up studies (Anton et al., 2001, and O'Malley et al., 1996) and the study of O'Malley et al., 1995 were excluded from methodological quality assessment.

4.3.6. Opioid studies: concomitant psychosocial treatments

The co-interventions in the treatment of opioid dependence widely varied, which complicated the evaluation of the additional effect of these co-interventions. In four studies only NTX was provided (Brahen et al., 1977; Guo et al., 2001; Hollister, 1978; San et al., 1991). In one study operant analysis through reinforcement combined with NTX was analysed (Mello et al., 1981). In some other studies a psychosocial treatment, such as individual counseling, (supportive) group therapy and behavioral therapy was provided as a co-intervention (Lerner et al., 1992; Shufman et al., 1994). In sum, it was not possible to analyse the benefits of the included co-interventions for the opioid studies.

4.3.7. Alcohol studies: effectiveness of NTX (medium term)

Relapse rates were reported by almost all studies (except for Ahmadi and Ahmadi, 2002; Balldin et al., 2003; Lee et al., 2001). Fourteen studies provided sufficient data regarding relapse rates. Studies showed sufficient clinical homogeneity. The Q-test showed statistical heterogeneity [χ^2 = 21.25, d*f* 12, P = 0.05 (Figure 4.1)], but the forest plot did not show a wide variation in effect sizes and confidence intervals. Therefore, we calculated an overall effect estimate. The pooled difference in relapse rate was 13% in favour of NTX [(95% CI) 7% to 18%; NNT = 8; (Figure 4.1)].

Seven studies reported on continuous abstinence (Anton et al., 1999; Chick et al., 2000; Gastpar et al., 2002; Kranzler et al., 2000; Lee et al., 2001; O'Malley et al., 1992; Oslin et al., 1997). Both the forest plot and Q-test showed no significant statistical heterogeneity. The pooled difference in the proportion of participants remaining abstinent was 6% and not significant [(95% CI) –2% to 15%, P = 0.12, Q-test: χ^2 = 8.90, d*f 6*, P = 0.18 (Figure 4.2)].

Percentages of drinking days were provided by four studies. The forest plot and Q-test both demonstrated considerable heterogeneity (Q-test: χ^2 = 36.59, d*f* 4, P < 0.00001). Three studies reported a statistically significant difference in favour of

NTX, with differences in percentage of drinking days ranging between 2.7 and 6.7 (O'Malley et al., 1992; Volpicelli et al., 1992; Volpicelli et al., 1997). However, Krystal et al (2001) showed no significant differences in percentage of drinking days.

Time to first relapse was a study outcome provided in nine studies. Only two studies reported the standard deviation (SD) needed for pooling a continuous outcome (Anton et al., 1999; Krystal et al., 2001). Therefore statistical pooling was not possible. Five studies reported a statistically significant difference in favour of NTX (Anton et al., 1999; Guardia et al., 2002; Latt et al., 2002; Morris et al., 2001; Volpicelli et al., 1992). Four studies showed no statistically significant difference (Chick et al., 2000; Gastpar et al., 2002; Kranzler et al., 2000; Krystal et al., 2001).

Six studies reported on time to first drink, but only two studies reported the outcome with SDs, needed for statistical pooling (Anton et al., 1999; Guardia et al., 2002). Consequently, statistical pooling was not endorsed. In five of the six studies no significant difference was observed (Anton et al., 1999; Chick et al., 2000; Guardia et al., 2002; Kranzler et al., 2000; Morris et al., 2001). Only one study reported a statistically significant difference in favour of NTX (Kiefer et al., 2003).

We conclude that there is strong evidence that NTX is superior to placebo regarding medium term relapse rates. There is strong evidence that that there is no difference in terms of continuous abstinence. Based on a qualitative analysis, there is strong evidence in favour of NTX regarding percentage of drinking days, compared to placebo. There is conflicting evidence regarding time to first relapse, and there is strong evidence that there is no difference in time to first drink.

4.3.8. Alcohol studies: effectiveness of NTX (long term)

Six studies reported follow-up or long-term results (Anton et al., 2001, a follow-up study of Anton et al., 1999; Balldin et al., 2003; Heinälä et al., 2001; Krystal et al., 2001; O'Malley et al., 1996, a follow-up study of O'Malley et al., 1992; Oslin et al., 2002). Two studies were excluded from this analysis as they did not include a comparison between NTX and placebo comparison (Oslin et al., 2002) or targeted irregular NTX use, instead of maintenance (Heinälä et al., 2001).

Of the four remaining studies, two studies (Balldin et al., 2003; Krystal et al., 2001) reported no significant differences regarding time to first relapse and percentage drinking days. Two studies showed a significant difference in relapse rate in favour of NTX (Anton et al., 2001, and O'Malley et al., 1996).

The pooled weighted mean difference in percentage drinking days (Balldin et al., 2003; Krystal et al., 2001) was not statistically significant [2.75 (95% CI) -2.36 to 7.86; Q-test: $\chi^2 = 5.19$, d*f* 3, P = 0.16 (Figure 4.3)].

In sum, there is moderate evidence in favour of NTX concerning relapse rate. There is also moderate evidence that there is no difference in the long-term effects of NTX on percentage of drinking days and time to first relapse in alcohol dependent patients.

4.3.9. Alcohol studies: compliance of NTX

Partly due to a lack of available data, there was no statistically significant relationship between the effect sizes of the defined outcome measures as reported in Figure 4.2 and 4.3, and treatment retention over the studies. Nevertheless, several studies individually reported a significant interaction effect of NTX compliance on the relations between treatment condition and outcome (Chick et al., 2000; Kranzler et al., 2000; Krystal et al., 2001; O'Malley et al., 1992; Volpicelli et al., 1997). Volpicelli et al (1997) demonstrate a firm relationship between the beneficial effects of NTX in reducing alcohol relapse and compliance. Moreover, less compliant subjects do not show any effect from NTX treatment. This finding was supported by Kranzler et al (2000), who ascertained a link between NTX compliance and a decline in frequency of drinking, heavy drinking and average alcohol consumption. According to Chick et al (2000), a NTX compliant subgroup yielded greater reductions in total alcohol consumption, improvements in serum GGT activities, improvement in physicians' global rating of alcoholism severity and by greater reduction of craving compared to the less compliant subgroup. Krystal et al (2001) found that, independent of treatment assignment (NTX versus placebo), there is evidence that patients who are more compliant with prescribed medication, in general, attended more counseling sessions, and participated in more AA

meetings and in turn had better treatment outcomes. Despite the absence of a statistically significant correlation between treatment retention and effect size, we conclude that within several studies a specific relationship between NTX compliance and successful treatment outcome was observed, and that this finding may explain some of the negative findings and some of the heterogeneity in the findings regarding the effectiveness of NTX in the treatment of alcohol dependence.

4.3.10. Alcohol studies: concomitant psychosocial treatment

An overview of the co-interventions (frequency and interventions) used in the treatment of alcohol dependence is presented in Table 4.2. Almost all studies provided some form of additional psychosocial treatment. In general, the description of the psychosocial intervention was not detailed, although cognitive behavioral oriented treatments, including relapse prevention and coping skills, were used in most studies. In general, cognitive behavioral therapy (CBT) aims to reduce the chance that a slip or lapse may turn into a relapse (Anton et al., 1999). Studies generally referred to published manuals (e.g. Gorski & Miller, 1986; Kadden et al., 1992; Marlatt & Gordon, 1985; McCrady et al., 1985; Monti et al., 1986). Some other studies used supportive psychosocial treatments, designed to support the patient's own efforts at abstinence without teaching specific coping skills (e.g. O'Malley et al., 1992). The frequency of the co-interventions varied between once a week and daily. Types of treatments were individual counseling, group therapy, or a combination of both.

Several studies reported the surplus value of auxiliary psychosocial treatment (Anton et al., 1999; Balldin et al., 2003; Chick et al., 2000; Gastpar et al., 2002; Latt et al., 2002; O'Malley et al., 1992; Volpicelli et al., 1997). It was demonstrated that the cumulative rate of abstinence was highest for patients treated with NTX and supportive therapy (O'Malley et al., 1992). Conversely, NTX combined with CBT prevented slips from becoming relapses and produced the lowest cumulative rates of relapse if drinking occurred (O'Malley et al., 1992).

Figure 4.1. *Statistical pooling of the relapse rates for alcohol dependence (medium term).*

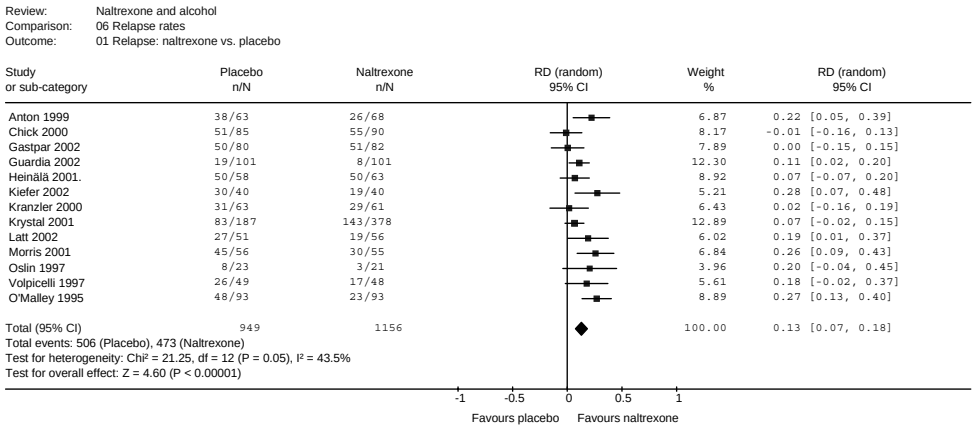


Figure 4.2. *Statistical pooling of the abstinence rates for alcohol dependence (medium term).*

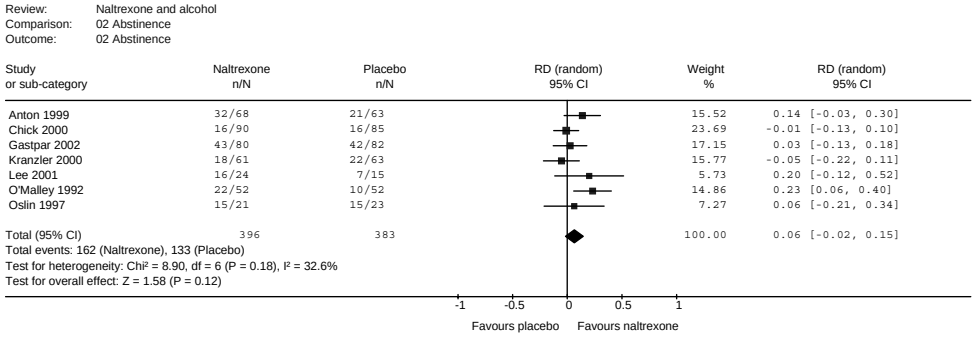
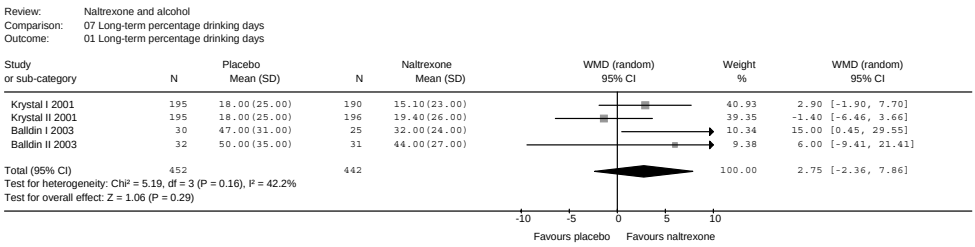


Figure 4.3. *Statistical pooling of the percentage drinking days for alcohol dependence (long term).*



Note: Four comparisons were extracted from two studies, due to the 2x2 factorial design

Table 4.2. *Study characteristics of the included alcohol studies and the co-interventions.*

Population							Outcomes						Co-interventions
Study	Duration (weeks)	Follow-up (weeks)	NTX	PI	Mean age (years)	Gender (% men)	Relapse rate	Abstinence	% drinking days	Time to first relapse	Time to first drink	Frequency	Interventions
Ahmadi 2002	12		58	58	42.7 ntx 43.2 pl	100	•	•				1/w	Through individual counseling sessions information about alcohol use, abuse and consequences of dependence are discussed. Additionally, training in relapse prevention through identifying situations, places and people that cue drinking behavior and by teaching patients techniques to either avoid or manage these situations.
Anton 1999[1]	12	14	68	63	41 ntx 44 pl	69 ntx 73 pl	•	•		•	•	1/w	Individual manual guided cognitive-behavioral therapy (Anton, 1996), which addresses issues of craving, management of slip drinking, reduction of relapses and other similar techniques.
Balldin 2003	26		56	62	50 ntx + cbt 48 ntx + st 50 pl + cbt 51 pl + st	84 ntx + cbt 87 ntx + st 77 pl + cbt 91 pl + st			•	•		9 sessions	Two types of co-intervention[6]: 1. Cognitive behavioral therapy (CBT) (Kadden et al, 1992): the therapy procedure includes instructions in self-monitoring and functional analyses of drinking behavior and urges to drink, developments of abstinence-oriented activities, and encouragement to develop strategies to keep a slip-up from developing into relapse. 2. Supportive therapy (ST) was defined as "the treatment as usual" and was performed at each site by the regular staff, who was experienced in the addiction field. Their main task was to be supportive and to motivate the patient into sobriety without teaching specific coping skills.
Chick[3] 2000	12		90	85	43.1 ntx 43.9 pl	72 ntx 78 pl	•[4]	•		•[5]	•[5]		Each site provided its usual psychosocial alcohol treatment program. No protocol constraints for type and amount of treatment.
Gastpar[3] 2002	12		84	87	43.4 ntx 42 pl	77 ntx 68 pl	•	•		•[5]		1/w	Each site provided its usual psychosocial alcohol treatment program
Guardia 2002	12		93	99	41 ntx 42 pl	72 ntx 77 pl	•			•[5]	•	1/w	Supportive group therapy for relapse prevention and individual supportive counseling
Heinälä 2001	12	32	63	58	45.5 (total sample)	86 (total sample)	•[4]					1/3w	Two types of co-intervention[6]: 1. Cognitive behavioral therapy in a group setting (manual guided). The emphases on coping with a slip when the patient samples alcohol so as to prevent it from proceeding on to a binge of drinking. 2. Supportive group, emphasis on support of complete abstinence from all drinking.

Population							Outcomes						Co-interventions
Study	Duration (weeks)	Follow-up (weeks)	NTX	Pl	Mean age (years)	Gender (% men)	Relapse rate	Abstinence	% drinking days	Time to first relapse	Time to first drink	Frequency	Interventions
Kiefer, 2003	12		40	40	46.6 ntx 45.6 pl	78 ntx 68 pl	•[4]				•[5]	1/w	Group therapy included coping skills and relapse prevention based on the cognitive behavioral model of substance abuse. The main components of the program were screening of the week before for thoughts on alcohol intake or subjective feelings of craving, intending to identify alcohol-associated stimuli and high-risk situations, and anticipating risk situations to prepare coping strategies.
Kranzler, 2000	11		61	63	39.7 ntx - pl	80 ntx	•	•		•[7]	•	1/w	Manual guided coping skills training after methods of McCrady et al. (1985) and Monti et al. (1986). Interventions were designed to foster problem solving, interpersonal skills, relaxation and coping skills for craving and urges. Participants learned to identify and handle situations that created a high risk for the resumption of drinking.
Krystal, 2001	13	52	378	187	49 ntx 49.5 pl	97 ntx 99.5 pl	•		•	•		1/w	12-step facilitation counseling encompassed reinforcing abstinence, providing basic relapse-prevention information, promoting acceptance of drug therapy and reducing attrition (Project MATCH, 1993). In addition attending Alcoholic Anonymous (AA) meetings were encouraged.
Latt, 2002	12		56	51	44.8 (total sample)	69 (total sample)	•			•[5]			Patients were encouraged to attend counseling and/or Alcoholics Anonymous. This was not obligatory.
Lee, 2001	12		35	18	45 (total sample)	100		•					First month: total abstinence, 12-step based primary rehabilitation program (Lee, 1997) throughout their 1-month stay, i.e. daily lectures and small topic group discussions, twice-weekly group psychotherapy sessions, thrice-weekly support group meetings, thrice-weekly video sessions and recreational therapy, reading and writing assignments and an optional attendance at AA. After 1 month: two-weekly follow-up with psychiatrist with encouragement to attend regular outpatient group therapy, support group and AA meetings.
Morris, 2001	12		55	56	48 ntx 47 pl	100	•			•[7]	•[5]	1/w	Manualised group psycho education and social support encompassed training in relapse prevention through identifying situations, places and people that cue drinking behavior and teaching techniques to either avoid or manage these situations. Patients were encouraged to support each other and talk in the group about their progress (Morris et al, 2001).

Population							Outcomes						Co-interventions
Study	Duration (weeks)	Follow-up (weeks)	NTX	Pl	Mean age (years)	Gender (% men)	Relapse rate	Abstinence	% drinking days	Time to first relapse	Time to first drink	Frequency	Interventions
O'Malley, 1992[9]	12	26	52	52	40.5 (total sample)	74% (total sample)	•[8]	•	•				Two types of co-intervention[6]: 1. Coping skills/relapse prevention therapy was basedon the cognitive-behavioral model of substance abuse of Marlatt and Gordon (1985). Main components of the program are self monitoring and functional analysis of drinking behavior and urge to drink, training and rehearsal of anger management, cognitive and behavioral coping strategies, instruction in problem-solving and decision-making skills. 2. Supportive therapy: patients were encouraged to remain abstinent without being taught specific coping skills. Support and advice if asked by the patient.
Oslin, 1997	12		21	23	56.5 ntx 58.9 pl	100	•	•				1/w	In addition to group therapy meetings with a case manager were provided at least twice a month. The goal of psychosocial treatment was to achieve abstinence through peer support and education.
Volpicelli, 1992	12		35	35	43.5 ntx 43.3 pl	100	•[8]		•	•[5]		Daily 2/w	First month: daily treatment, group therapy, individual counseling, educational classes, recreation, health education and general health care. After 1 month: group therapy
Volpicelli, 1997	12		48	49	39 ntx 37.9 pl	73.5 ntx 82 pl	•		•	•[5]		First month: 2/w After 1 month: 1/w	Individual psychotherapy modelled after Gorski and Miller's relapse prevention program (1986).

Note: studies are described by author and year, duration and follow-up is mentioned in weeks, number of patients that are either allocated to the NTX or placebo condition (NTX, PL), mean age in years, gender by percentage men. Outcomes: relapse rate; relapse is defined as 5 or more drinks per day for men and 4 or more drinks per day for women. Other outcome rates are abstinence, percentage drinking days, time to first relapse and time to first drink. Co-interventions: frequency of the co-interventions and a description of the intervention. Abbreviations: NTX, naltrexone; PL, placebo; w, weeks; 1/w, weekly; 2/w, two times a week; 1/3w, one time per three weeks. 1). Anton et al. (2001) is the follow-up study of Anton et al. (1999). 2). Three study groups: long-term NTX (52 weeks), medium-term NTX (13 weeks) and placebo (52 weeks). 3). Multicentre study. 4). Outcome rates were assessed through graphical inspections. 5). Standard deviation (SD) was not provided. 6). The NTX and the placebo group were allocated to receive either cognitive-behavioral oriented or supportive treatment. 7).Time to first relapse is reported in weeks without SDs. 8). The combined outcomes of the two trials (O'Malley et al., 1992, and Volpicelli et al., 1992) are reported in O'Malley et al. (1995). 9). O'Malley et al. (1996) is the follow-up study of O'Malley et al. (1992).

This finding was confirmed by Balldin et al. (2003), in which the time to first relapse was longer for the group treated with CBT when compared to supportive therapy. Similar outcomes were observed in the study of Heinälä et al. (2001), where NTX combined with CBT was better than NTX combined with supportive therapy. In this respect it is suggested that cognitive behavioral treatments improve NTX treatment effectiveness (Anton et al., 1999, Balldin et al., 2003, Heinälä et al., 2001; O'Malley et al., 1992).

4.3.11. Alcohol studies: subgroup analyses

Subgroup analyses were performed addressing the surplus value of NTX in combination with different types of psychosocial treatment. Four studies used individual treatment such as relapse prevention or cognitive behavior therapy (Anton et al., 1999; Kranzler et al., 2000; Krystal et al., 2001; Volpicelli et al., 1997), and four studies applied group psychotherapy (Kiefer et al., 2003; Morris et al., 2001; Oslin et al., 1997; Volpicelli et al., 1992). The pooled difference in relapse rate for NTX in combination with individual treatment was 13 % [(95% CI) .05 to .20; NNT = 8; Q-test: χ^2 = 12.18, d*f* 7, P = 0.095] and the pooled difference of NTX embedded in group therapy was 20 % [(95% CI) .09 to .30; NNT = 5; Q-test: χ^2 = 4.91, d*f* 3, P = 0.18]. Meta-regression analyses showed that these subgroup effects, the comparison between individual and group treatment, were not statistically significant. Further subgroup analyses were not possible due to a lack of available data for comparison.

4.4. Discussion

We conducted a review on the effectiveness of NTX in the maintenance treatment of opioid and alcohol dependence. Where possible, studies were statistically pooled using the random effect model. This model takes into account the within-study sampling error and between-studies variation.

4.4.1. Opioid dependence: effectiveness of NTX maintenance

The small number of available opioid studies showed wide variation regarding population and interventions. Consequently, the studies could not be statistically pooled. Overall, treatment with NTX may be slightly more favourable when compared to placebo, but due to clinical heterogeneity, there is insufficient evidence to confirm of refute the effectiveness of NTX in the treatment of opioid dependence. This result is in concordance with other reviews (Kirchmayer et al., 2004), despite one added recent study (Guo et al., 2004). We did not find a meaningful relationship between treatment retention and effect size in the included opioid studies. Furthermore, it was not possible to evaluate the additional effect of psychosocial therapy in the opioid studies. Often NTX was provided as a mono-therapy. The other included studies used different sets of techniques to assist the participant.

4.4.2. Opioid dependence: NTX in combination with psychosocial interventions

Several studies, not included in this review, have suggested that NTX combined with psychosocial interventions is superior to NTX alone (Callahan et al., 1976; c.f. Carroll et al., 1997; Resnick et al., 1979, 1981; Stone-Washton et al., 1982). More recent research has demonstrated that the combination of NTX with psychosocial treatment may be an effective approach only for specific (highly motivated) groups or in controlled settings or conditions (cultural or/and family involvement) to monitor compliance, such as health professionals and federal probationers (Cornish et al., 1997; Fals-Stewart et al., 2003; Kirchmayer et al., 2003; Krupitsky et al., 2004; Ling & Wesson, 1984; Washton et al., 1984).

4.4.3. Alcohol dependence: effectiveness of NTX maintenance

This review demonstrated that NTX is effective in the treatment of alcohol dependence, especially with regard to the primary outcome parameter, i.e. relapse into heavy or uncontrolled drinking. We included seven additional recent studies (Ahmadi and Ahmadi 2002; Balldin et al., 2003; Gastpar et al., 2002; Guardia et al., 2002; Kiefer et al., 2003; Latt et al., 2002; Lee et al., 2001) compared to the most recent update of the Cochrane review (Srisurapanont & Jarusuraisin, 2004). Our results corroborate the outcomes of the previous reviews on NTX and alcohol dependence (Bouza et al., 2004; Fiellin et al., 2000; Garbutt et al., 1999; Kranzler & Van Kirk, 2001; Miller & Wilbourne, 2002; Sinclair, 2001; Srisurapanont & Jarusuraisin, 2004; Streeton & Wheelan, 2001; Swift, 1999).

Although most of the pooled estimates were statistically significant (*medium-term*: relapse rate, continuous abstinence, percentages of drinking days, time to first relapse; *long-term*: relapse rate), some results showed considerable statistical heterogeneity (medium term: relapse rate, percentage of drinking days). This heterogeneity may be partly explained by differences in variables such as compliance, co-interventions (frequency and type of interventions) and characteristics of the study population.

Although the pooled effect sizes may be considered to be rather modest, they are of the same magnitude as other psychopharmacological agents such as TCAs and SSRI's in the treatment of major depression (Lima & Moncrieff 2000; Storosum et al., 2001). It should be noted that NTX studies in alcohol dependent patients were virtually all supported by non-pharmaceutical sources and thus have a smaller likelihood of selective publication of only positive studies.

4.4.4. Compliance with NTX treatment

To evaluate compliance, we estimated the relationship between effect size and treatment retention. In general, studies reported on treatment retention and not directly on NTX compliance. In addition, the studies that did report on NTX

compliance used a wide variety of methods to measure compliance, such as pill-count, the inclusion of riboflavin in NTX capsules, and self-reports. Furthermore, the reported compliance rates were measured at different follow-up periods and using different statistical methods.

Analyses of compliance measured, as the relationship between treatment retention and effect size, yielded no positive results. These negative findings may be due to 'aggregation bias' or 'ecological fallacy' (Morgenstern, 1982), as the relationship with participant averages across trials may deviate from the relationship for participants within trails, and without individual data cannot be investigated (Thompson & Higgins, 2002). Indeed, several individual studies did report statistically significant findings (Chick et al., 2000; Kranzler et al., 2000; Krystal et al., 2001; O'Malley et al., 1992; Volpicelli et al., 1997). Consequently, we conclude that NTX compliance probably is pivotal for successful alcohol treatment.

4.4.5. NTX in combination with psychosocial interventions in alcohol treatment

It is suggested that there is added value of auxiliary psychosocial treatment, and therefore NTX treatments should be delivered in concert with psychosocial interventions (Srisurapanont & Jarusuraisin 2004). Nearly all studies on NTX embedded NTX in a cognitive-behavioral oriented program (Table 4.2). A systematic exploration of the influence of psychosocial co-intervention was hindered by sketchy descriptions of these treatments. Consequently, the content of CBT and supportive therapy was often unclear. Nevertheless, based on the current data, there is some evidence that the combination of NTX with CBT is somewhat more effective than NTX combined with supportive therapy. NTX and CBT both target to prevent slips from becoming relapses and therefore might have synergistic effects, but it is not possible to draw firm conclusions on the possible auxiliary benefits of these psychosocial interventions.

Nowadays, cognitive-behavioral interventions, such as teaching coping skills and relapse prevention are considered as top-ranked treatment modalities (Miller & Wilbourne 2002). It should be noted, however, that some groups, such as older

adults, appear to respond well to a medically oriented program that is rather supportive and individualised (Oslin, Pettinati & Volpicelli, 2002).

Subgroup analyses suggested a difference in effect in favour of NTX when combined with group therapy. The difference between group therapy and individual or other treatment was, however, not statistically significant. The meta-regression analysis was hindered by the lack of statistical power (only four studies per subgroup).

4.4.6. Long-term effects of NTX

In general, the studies reported on the medium-term effects (i.e. 12-13 weeks) of NTX. Evaluations of placebo controlled NTX maintenance programs on the long term are rather scant, especially for opioid studies. Due to insufficient data, no firm conclusions can be drawn with regard to the effects of NTX after discontinuation. However, it is tempting to argue that NTX, just like other medications such as antipsychotics and antihypertensives, does not foster sustained remission after discontinuation, as chronic disorders need continuous treatment (McLellan, 2002). This would suggest that NTX should be prescribed over a long period of time.

4.4.7. Methodological quality

In general, the methodological quality of the included studies just exceeded the threshold of 50% (> 8). In most studies the scores regarding methodological quality were suppressed due to inadequate description of randomisation, intention-to-treat analysis, and allocation concealment criteria. Furthermore, many studies showed dropout rates, which exceeded the threshold of 20%. The loss to follow-up and the high drop out rates (attrition bias) produce a substantial problem, as retention itself is often one of the primary outcomes.

All included opioid studies fulfilled the criterion of an adequate blinding. It should be noted, however, that blinding of patients in an opioid NTX–placebo trial is virtually impossible. Participants can easily trace their allocated condition by a

heroin challenge test. NTX was approved by the FDA based on its pharmacological efficacy without any positive double blind studies because of the above-mentioned blinding problems. A third condition (no treatment) can be added to resolve some of the methodological issue.

4.4.8. Limitations of this review

This review has a few important limitations. We did not consult the authors to receive either additional information on methodological aspects of their study, or additional (statistical) information when it was not reported in their studies. Supplementary information on methodological assessment might have resulted in (slightly) higher method scores. The number of studies that provided statistical data needed to perform quantitative analyses limited the actual performed analyses, as we had to eliminate several studies from the meta-analyses due to a lack of available data or because the standard deviations (SD's) were not provided. Therefore, the results might be slightly skewed and this might attenuate the validity of the conclusions.

In general, the performed meta-analyses were based on intention to treat (ITT) analyses, although several studies did not report ITT data suitable to conduct statistical analyses. We often chose to extract reported outcomes based on smaller sample sizes than the initial number of randomised participants (Chick et al., 2000; Gastpar et al., 2002; Guardia et al., 2002; Krystal et al., 2002). This might have resulted in improved outcomes in favour of NTX. Due to inclusion of other studies in the analyses this limitation is not substantial and probably does not affect the conclusions.

4.4.9. Safety of NTX

Exploring the literature, we encountered several publications dealing with safety issues, which may be important for use of NTX in regular clinical practise. There are three remarks to make.

It must be noted that NTX itself has virtually no abuse potentials and is not characterised by tolerance. It has been argued that NTX has the capacity to produce dose related hepatocellular injury. Nevertheless, there is virtually no evidence that NTX causes clinically significant liver disease or exacerbates, even at high doses, serious pre-existing liver disease (Brewer & Wong, 2004).

Currently, there are some reports of serious adverse events and even deaths, which are attributed to rapid detoxification procedures (Dyer, 1998; Kaye et al., 2003; Pfab et al., 1999; Roozen et al., 2002; San et al., 1995). It is important to note that NTX has no approval for rapid opioid detoxification in the US and EC, though it has been used for that purpose. The method is surrounded with a variety of opinions, as there is lack of agreement about the treatment and evidence on the long term (Singh & Basu, 2004).

Warnings have been issued regarding the overdose risk following NTX discontinuation in the treatment of opioid dependent patients. Receptor hypersensitivity followed by tolerance reduction could increase the risk of a fatal heroin overdose (Lesscher et al., 2003). However, a retrospective study showed no significant difference in overdose deaths between a NTX-exposed and a non-exposed group of deaths (Arnold-Reed et al., 2003). Conversely, a recent large longitudinal study, based on data from 12 trials, ascertained that individuals who leave pharmacotherapies for opioid dependence experience higher overdose and death rates compared with those in treatment. Accordingly, NTX treatment patients should be warned about heroin overdose risks (Digiusto et al., 2004; Ritter 2002).

4.4.10. Options to increase the effectiveness of NTX

Several strategies and hypotheses have been brought up in the literature, in which NTX compliance is subject of debate. Recently, Weiss (2004) suggested three strategies to improve the effectiveness of pharmacotherapy in the treatment of patients with alcohol and drug dependence: (1) interventions that can be used by the clinician in individual sessions, (2) the inclusion of external reinforcements

(positive and negative contingencies) and involvement of family members or significant others and (3) medication prescribing and dosing strategies.

Individual sessions should focus on a collaborative approach to create a treatment plan that addresses the cost/benefit ratio of improved outcome by NTX. Patients who are adherent are considered as acting on a consensual agreed-upon plan that they have had a part in designing, or at least as accepting the importance of performing the recommended treatment actions (DiMatteo & DiNicola, 1982). In this respect interventions aimed at enhancing medication adherence should specifically target the patient's beliefs and attitudes concerning the illness and medication and should not be in conflict with subjects' personal goals (Patel & David, 2004).

A second option concerns the inclusion of external reinforcements. Linked to the Community Reinforcement Approach (CRA), an adjunctive instructional program for improving compliance can be used (Azrin & Teichner, 1998). It can be employed to encourage taking NTX under supervision (of significant others) to increase treatment adherence (Meyers & Smith, 1995; Roozen et al., 2003). In addition, Contingency Management (CM; Higgins et al., 2004) can enhance compliance and increase the effectiveness of NTX (Carroll et al., 2001; Carroll et al., 2002; Preston et al., 1999). Both CRA and CM are based on the learning theory derived from the operant reinforcement approach designated by Skinner (Skinner, 1938). NTX fits well in this framework as NTX directly competes with positive reinforcement induced by the use of opioids and alcohol.

A third opportunity is aimed to increase the likelihood of taking NTX. "Pill-count" or medication usage skills for effectiveness program (e.g. MUSE-P) can improve medication compliance through a feedback system. Feedback is given by medication bottles with micro-electronic monitor caps that record the date and time of each opening and display the number of hours passed since the previous opening (Cramer 1998; Cramer & Rosenheck 1999). A pharmacological route, as a dosing strategy, to govern adequate plasma concentrations of NTX seems to be the insertion of NTX implants or depots (Carreno et al., 2003; Foster et al., 2003; Kranzler et al., 2004) to treat both alcohol and opioid use disorders.

4.4.11. Predictors of NTX' effectiveness

Recently, there is an increase in interest to predict the effectiveness of NTX, which is important to explain the variability in outcome in the current literature. It is ascertained that genetic polymorphism programming the μ-opioid receptor might play a pharmacogenetic role in the differential response to an antagonist (Oslin et al., 2003, Oswald et al., 2004). Other alcohol studies on predictors of clinical effectiveness of NTX suggest that participants with an older age, high levels of alcohol craving, a strong family history of alcohol use disorders, high levels of somatic distress, and low educational level are more likely to benefit (e.g. Flannery et al., 2003; O'Mallley et al., 1996; Oslin, Pettinati and Volpicelli, 2002; Monterosso et al., 2001; Volpicelli et al., 1995).

Studies on opioids showed that young participants, a low level of dependence, employment, being married, and length of NTX therapy were related to better outcome (Greenstein et al., 1983; McGregor et al., 2002). A high score on cluster-B personality disorders and polydrug use is associated with relapse in NTX opioid treatment (Roozen et al., 2003).

4.4.12. Conclusions and recommendations for future research

We conclude that NTX, at least based on the pharmacological profile, is a viable agent in substance use disorders including opioids and alcohol. Blinding problems in the classic way and insufficient data afflict the assessment of effectiveness in opioid dependence. Therefore, up to now, there is insufficient evidence to support maintenance treatment in opioid dependent patients. In contrast, this review confirms the effectiveness of NTX in the maintenance treatment of alcohol dependence.

In general practice, it is crucial that patients take NTX as prescribed in order to control safety issues and to evaluate the effectiveness of NTX, properly. Therefore it is warranted to pursue avenues of research to prevent drop out and to ameliorate treatment compliance. Future studies on both alcohol and opioid disorders ought to

seek the identification of the cognitive-motivational rationale (adherence) concerning the NTX treatment regimen. In combination with reports on side effects, craving and urinalyses on both NTX and its' active metabolite (i.e. 6-β-naltrexol) related to alcohol consumption or opioid metabolites (i.e. 6-monoacetylmorphine) may provide more awareness into the potential mechanisms of action of NTX, in terms of discontinuation, relapse, and resuming alcohol or opioid use.

More RCTs with longer treatments are recommended, particularly because addiction is viewed as a chronic relapsing disease (Leshner, 1997; McLellan, 2002; Van den Brink & Van Ree, 2003). Finally, to gain more information on the effects of NTX after discontinuation longer follow-up periods are needed.

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CHAPTER 5

Experiences with an outpatient relapse program (Community Reinforcement Approach) combined with naltrexone in the treatment of opioid-dependence: effect on addictive behaviors and the predictive value of psychiatric comorbidity

Abstract

There is increasing interest in naltrexone, an opiate antagonist, in the treatment of opiate addicts. The effects of naltrexone are often compromised by a lack of compliance and drop-out. The effects of this compound are probably more favorable when combined with a psychosocial intervention such as Community Reinforcement Approach (CRA). To explore the effects of a combination therapy (naltrexone plus CRA treatment) and the predictive value of sociodemographic and psychopathologic characteristics. Using a before-and-after design, heroin addicts (n = 24) receiving a combined naltrexone plus CRA treatment are compared with a group (n = 20) on methadone maintenance therapy (reference group). Over a period of 6 months, 58% (14/24) did not relapse, after 1 year at least 55% (12/22) still met the initial goal of continuous abstinence. At baseline, the treatment group and the reference group were similar on nearly all variables except for the number of times clients were arrested. Within the treatment group, a comparison was made between the continuous abstinent and those who relapsed into frequent opioid use. Differences were significant in the cluster-B personality disorders and in polydrug users. The combination of naltrexone plus intensive CRA in an outpatient setting appears to be promising. A high score on cluster-B and polydrug use is associated with relapse.

5.1. Introduction

In the field of opiate addiction treatment, there has been an increase in the use of pharmacological compounds such as naltrexone. After induction, this agent can be effective in the prevention of recurrent heroin use. During naltrexone maintenance treatment, the effects of heroin will be blocked, leading to lesser anticipation of the desired effects and a decrease in the relapse rate.
Similar to other forms of therapies aimed at abstinence, patient compliance is often a problem and many patients relapse after having discontinued taking medication (American Psychiatric Association, 1995).
One study (Washton et al., 1984) showed good results with naltrexone (61% abstinence after 6 months) with highly motivated participants, such as business people and doctors. In addition, in southern Europe, good results with naltrexone (40 % abstinence after 6 months treatment) have been reported (Guiteirrez et al., 1995). The result is attributed to traditional family structure and other forms of social interactions that increase treatment compliance. These findings suggest that a combination of naltrexone maintenance and psychosocial therapy may lead to an increase in therapy compliance and a decrease in the relapse rate.

A promising approach is the Community Reinforcement Approach (CRA) (Meyers & Miller, 2001). CRA encompasses elements such as social network and enhancing motivation and is often supported by a variety of pharmacological interventions (i.e. naltrexone) and procedures to enhance compliance with the recommended medication regimen. First, there are interventions aimed at enhancing the social network (for example interventions including partners and parents, aimed at compliance). CRA pays attention to the expectations, motivation, coping skills, social, labor and recreational elements.

However, combined forms of therapy also suffer often from early dropout and lack of therapy compliance. An important factor, which effects compliance and dropout, is psychiatric comorbidity (Kranzler & Rounsaville, 1998). In general the severity of psychiatric symptoms worsens the prognoses (McLellan et al., 1983).

Research suggests that the prevalence of psychiatric disorders among heroin addicts is high. There is a relationship between drug addiction and depression, anxiety and personality disorders (Verheul et al., 2000). Personality disorders are seen as negative predictors of treatment outcome (De Jong et al., 1993).

The aim of this open-label study is to optimize the effects of using a combination of CRA and naltrexone.The present study consists of a naturalistic follow-up study with before-and-after comparison without a control group. In order to assess a possible generalization of the study, a comparison on relevant variables was made with a group of heroin addicts participating in a methadone maintenance program.
The following questions were addressed: (1) is the study population comparable to the group of addicts participating in a methadone maintenance program; (2) what is the outcome in heroin addicts treated with naltrexone plus CRA, and (3) what is the predictive value of sociodemographic characteristics and psychiatric comorbidity in patients treated with naltrexone plus CRA?

5.2. Methods

5.2.1. Study Population

The treatment group consists of 24 heroin addicts treated with naltrexone in a CRA program from February 1996 until evaluation in May 1998. The treatment took place at the outpatient treatment center for addiction KENTRON in Roosendaal (< 100.000), the Netherlands. Subjects were recruited from methadone programs through newspaper articles and via addiction clinics throughout the Netherlands. During the research period 60 persons showed interest in participating by at least one contact. 24 persons were included (40%).

All 24 subjects were opiate-dependent and 21 of these were participants in a methadone program. Subjects were included during a 24-month period. Table 5.1 shows that follow-up varied between 6 and 24 months (mean length of treatment 16.6; SD = 5.3 months).

Detoxification of 19 subjects consisted of a rapid detoxification procedure (Roozen et al, 1997). In this procedure naltrexone was administered in increasing dosage: 12.5 mg/day on day 1, 25 mg/day on day 2, and up to 50 mg/day on days 3 and 4. To ameliorate withdrawal symptoms clonidine, diazepam, midazolam and ondansetron were used as indicated. The other 5 patients were detoxified by a methadone-tapering procedure either in a regular clinic or at home. Patients from the latter group had to pay a fee of Eur 227.00 (n = 5), and patients from the rapid detoxification program had to pay an extra fee of Eur 1,818.00 (n = 19).

Detoxification was followed by naltrexone maintenance. Subjects were stimulated and expected to bring a non-using partner, spouse or good friend to assist as a coach during detoxification and aftercare treatment. To check selection bias, a reference group of 20 participants randomly drawn from a regular methadone program was selected.

5.2.2. Intervention

After naltrexone induction, all subjects received a maintenance dosage of naltrexone of 25 mg/day. The treatment consisted of medical support, psychosocial interventions followed by a consistent and strict policy towards compliance (naltrexone) and control of substance abuse by urine analysis. The importance of the social network was emphasized. CRA implemented: diagnostic interview (functional analysis), psycho-education, pharmacotherapy, compliance therapy, urine analyses/monitoring, marriage/relation therapy, and support of the social network, career orientation, job counseling, education and hobbies, problem solving, social skills and cognitive restructuring.

The therapist (first author) has several years experience in the addiction setting. On regular basis, he received supervision from the second author and from multidisciplinary coworkers. The CRA program was tailored to the work of Meyers and Smith (1995). Treatment integrity was guarded on the basis of monitoring forms and stored in files. Data collection, extraction and interviewing was done by an independent researcher.

During the first month of treatment, counseling sessions averaged 2-3 sessions of 45 min/week, which was reduced to 1 weekly session of 45 min after 3-6 months, and, during the last phase, to monthly sessions. After 9 months the dosage of naltrexone was reduced to 12.5 mg/day. Abstinence was verified by means of controlled urine analyses.

5.2.3. Assessment Procedure

Subjects in the treatment group were interviewed prior to detoxification regarding baseline characteristics. The reference group was assessed in the same way.

5.2.4. Instruments

The following questionnaires and tests were included in this study: (1) SCL-90 (Symptom Check List; Derogatis, Lipman & Covi, 1973); (2) ABV (Amsterdamse Biografische Vragenlijst; Wilde, 1970); (3) VKP Questionnaire on Personality Traits (Vragenlijst Kenmerken van de Persoonlijkheid; Duijsens et al. 1993), and (4) the VGIT, the shortened version of the GIT (Groningse Intelligentie Test; Luteijn & Kooreman, 1987);

1. The SCL-90 is a multidimensional self-report on mood and somatic complaints. This list has been translated into Dutch (Arrindell & Ettema, 1981). There is a relationship between the scales of depression and anxiety in the SCL-90 and relevant categories in the DSM-III(R) (Koeter, 1992). The SCL-90 has proven to be a reasonable indicator of the severity of psychopathology among psychiatric patients (Koeter, Ormel & Van den Brink, 1988).
2. The ABV is a personality questionnaire measuring the dimensions: N = neurotic instability; NS = neurotic somatic complaints; E = social extravertism, and T = test attitude. The T dimension ranges from a self-criticizing attitude (low score) to a self-defending attitude (high score) in

answering the questionnaire. The N and NS scales are highly inter-correlated. The test-retest index is satisfactory (De Zeeuw, 1986).

3. For the presence and severity of personality pathology the VKP was used. This self-reporting questionnaire is based on the International Personality Disorder Examination (IPDE) of the WHO (World Health Organization, 1993). The VKP provides severity ratings on all 13 DSM-III-R (American Psychiatric Association, 1987) personality disorders. An important advantage of the VKP (next to cost-effectiveness) is the fact that during testing there is no systematic bias or interview tendencies (Zimmerman, 1994). Compared to an interview, the VKP has a high sensitivity and a low specificity.
4. VGIT: in this study intelligence was tested by using the short version of the GIT (Luteijn & Kooreman, 1987) consisting of the 3 subtests: numerical, a card lay puzzler and a word puzzler. The short version correlates 0.91 with the complete version (10 subtests) of the GIT. The results can be translated into an IQ score (De Zeeuw, 1986).

5.2.5. Statistical Analysis

To assess the predictive value of psychiatric co-morbidity comparisons were made between the abstinent and relapsed group concerning sociodemographic background, intelligence, juridical conflict, psychopathology and personality disorders. Differences in the means of continuous variables were tested by using the Student's t test. χ^2 statistics and Fisher's exact test (two-sided) were used to test differences in categorical data. Because of the small sample size and the explorative nature of the study, the significance level was set at $P < 0.05$.

5.3. Results

5.3.1. Comparison of treatment group with regular methadone clients

Table 5.1 shows that the 2 groups are similar on all variables except for the number of times clients were arrested (96% naltrexone versus 57% methadone $P < 0.05$).

Table 5.1. *Characteristics and psychopathology among naltrexone- and methadone population*.

	Population				P
	naltrexone (n=24)		methadone (n=20)		
	Mean	SD	Mean	SD	
Age, years	30.5	6.4	29.9	7.1	NS
Age onset opiate addiction, year	21.7	4.5	23.0	5.3	NS
Duration addiction, years	8.8	6.0	7.0	8.0	NS
Daily amount heroin, g	0.6	0.7	0.8	0.8	NS
Daily amount methadone, mg	24.8	10.6	25.7	9.0	NS
Mean IQ	102	10.6	90	13.5	NS
Polydrug users, %	67		91		NS
Women, %	13		18		NS
Min. once arrested, %	96		57		< 0.05
Min. once detention, %	58		43		NS
Min. once suicide attempt, %	35		29		NS
Clients with partner, %	63		57		NS
Clients with occupation, %	43		57		NS
Subscale SCL-90	(n=24)		(n=16)		NS
Anxiety	15.3	5.5	17.1	6.6	NS
Agoraphobia	8.7	3.0	10.6	4.7	NS
Depression	33.0	12.7	34.9	13.4	NS
Som. complaints	21.6	8.6	22.9	9.0	NS
Insufficiency	16.5	5.1	17.4	6.0	NS
Sensitivity	31.2	11.0	31.6	11.6	NS
Hostility	10.3	3.9	9.3	4.6	NS
Insomnia	6.9	3.3	7.2	3.8	NS
Other	14.3	4.9	14.8	5.6	NS
Total	157.6	47.8	165.8	54.1	NS
Subscale ABV	(n=24)		(n=16)		
N	69.5	31.6	55.3	27.8	NS
NS	24.3	9.1	23.3	8.9	NS
E	60.8	16.9	52.3	17.5	NS
T	32.7	7.9	37.3	8.3	NS

Note: Displayed are numbers, percentages, mean scores, standard deviations and significant levels ($P < 0.05$) for subscales and total scores of the SCL-90 and ABV.

5.3.2. Treatment outcomes of the naltrexone group

After a 6-month treatment period, 14 of 24 clients were still abstinent (58%). After 1 year, 12 of 22 were still abstinent (55%). One client used heroin incidentally after detoxification without relapse into frequent opiate abuse. All 10 clients, who relapsed into frequent opiate abuse, did so within 7 months after the start of treatment (Table 5.2).

Table 5.2. *Retention characteristics of the treatment population.*

Naltrexone plus CRA population		
Number of clients who relapsed	10/24 (42%)	
Number of clients who were abstinent after:		
Mean ≥ 6 months	14/24 (58%)	
Mean≥ 12 months	12/22 (55%)	
Mean length of treatment	16.6 (months)	SD = 5.3; min 6, max 24
Mean time to first relapse	3.8 (months)	SD = 2.4; min 1, max 7

Note: Displayed are numbers, percentages, means, standard deviations, minimal and maximal values.

Of 11 frequent cocaine users, 9 used cocaine a couple of times during treatment. One of them had a period of some weeks of extensive cocaine use. In that scenario the treatment was intensified and adapted to cocaine use, which ceased. Three clients who regularly used amphetamines ceased using this drug. One of them started taking drugs again after 5 months in treatment, but ceased using the substance again after 9 months. Of 8 benzodiazepine users, 6 stopped their benzodiazepine use. One of them persisted in irregular use of benzodiazepines, another slowly decreased his use to a stable maintenance level. The use of cannabis remained the same for almost all clients.

5.3.3. Predictive value of sociodemographic characteristics and psychiatric comorbidity

The abstinent (n = 14) and relapsed clients (n = 10) were compared with regard to sociodemographic background, intelligence, social integration, juridical conflict, psychopathology and personality disorders. Of the 43 different comparisons made,

only three showed statistical significance: (1) 90% of the relapse population were poly-drug users compared to 50% in the abstinence group; (2) the T score of the ABV showed a small but significant difference, a highly critical self-evaluation indicates a risk of relapse, and (3) those who relapsed had a higher total score on the B-cluster personality disorder measured at a dimensional level (Table 5.3).

Table 5.3. *Personality pathology according to DSM-III(R) axis II as measured by VKP, among naltrexone plus CRA group both in abstinent- and relapsed population.*

Disorder	Dimensional score				P
	abstinent (n=14)		relapsed (n=10)		
	Mean	SD	Mean	SD	
Cluster A	5.2	3.8	5.6	4.7	NS
Schizoid	1.1	1.3	1.2	1.3	NS
Schizotypal	2.1	2.1	2.1	2.3	NS
Paranoid	2.1	1.3	2.3	1.6	NS
Cluster B	9.7	5.0	15.8	6.4	< 0.05
Borderline	2.4	1.8	3.7	2.1	NS
Antisocial	5.1	2.7	7.1	2.8	NS
Histrionic	0.9	1.4	2.0	2.1	NS
Narcissistic	1.4	1.6	3.0	2.4	NS
Cluster C	7.7	7.0	9.5	7.9	NS
Dependent	1.8	1.9	2.8	2.4	NS
Avoidant	1.8	2.2	1.8	2.4	NS
Obsessive-compulsive	1.9	2.1	2.4	2.3	NS
Passive-aggressive	2.2	2.1	2.5	1.6	NS
Appendix A					
Sadistic	0.7	0.7	1.1	1.2	NS
Self-defeating	1.9	1.9	2.7	2.1	NS

Note: Displayed are means, standard deviations and significance levels (P < 0.05) of the dimensional scores and cluster total scores.

5.4. Discussion

The results of this pilot study, 55% drug free for a period of at least 12 months, are promising considering that this group of heroin addicts had a long addiction history and a long-term history of failed attempts to become abstinent. These results were achieved by rapid detoxification and by means of psychosocial outpatient treatment with naltrexone support. For the interpretation of these results it is important to investigate the selectivity of the treatment group. A comparison with a reference

group of methadone patients showed that both groups were similar. There was no difference as to drug abuse history and the amount and severity of (comorbid) psychopathology were not less in the naltrexone group. The only difference was the fact that the subjects participating in naltrexone treatment had been arrested more frequently than the subjects of the regular methadone program.

It is, however, likely that those subjects who applied for participation in the naltrexone group were more motivated than those participants following regular programs. Patients, in the treatment group could afford to pay a fee, or had a person in their network willing to pay for the treatment. Probably only a limited and selective proportion of heroin addicts maintain good contacts with non-addicts in order to find a non-drug using partner, spouse or friend willing to assist as a coach during treatment. In sum, participants in the naltrexone treatment group were probably better motivated and integrated in the community.

However, this can hardly be used as an objection against the study results, because motivating subjects is one of the key elements of the treatment as a whole. When the fee was a problem, or when the patient or the network was incapable of financing the treatment (objective information supporting their claim), there was a possibility of raising the complete amount of money from a charity foundation, from the municipality or from social benefits as a gift. Prior to acceptance, potential candidates and their coaches took part in a couple of informative meetings where they were motivated and prepared for treatment. It is the experience of the authors that this preparation prior to detoxification should not be underestimated.

As to any connection between the type of addict and success rate, we found that the risk of dropout was greatest among polydrug users, although even here 7 of the 16-polydrug users (44%) benefited from the treatment. In addition, cluster-B personality disorder was found to be an indicator for dropout, but was insufficient to be a contraindication for participation (c.f. Verheul, 1997).

Considering a 55% abstinence rate covering an average period of 12 months and comparing these results with other studies we find the results promising. Although it is tempting to credit the results to the applied intervention (naltrexone plus CRA), this is not possible until a randomized experimental design is followed.

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CHAPTER 6

High abstinence rates in heroin addicts by a new comprehensive treatment approach

Abstract

The objective of this study was to determine the effectiveness of a new combination of naltrexone maintenance combined with the Community Reinforcement Approach (CRA) in detoxified, opioid dependent patients. The design consisted of an open, naturalistic study following a RCT on the effectiveness of two methods of rapid detoxification. Four outpatient addiction treatment centres in the Netherlands participated.

272 detoxified patients were recruited from methadone maintenance programs. The intervention encompassed an outpatient treatment during 10 months, consisting of 13 sessions focusing on naltrexone compliance and 10 sessions according to CRA. The main outcome measures were abstinence for opioids and cumulative abstinence duration at 1, 10 and 16 months after detoxification. Secondary outcomes included health status, use of other psychoactive substances, addiction severity, craving, and general psychopathology. Follow-up data were available for 86% of the participants at 16 months. With intention-to-treat analysis, treatment yielded abstinence rates of 28% and 32% at 10 and 16 months. The cumulative abstinence rate at 16 months was 24%. Health related quality of life significantly improved more in the continuously abstinent group than in the relapsed group. In the abstinent group craving, general psychopathology, use of other psychoactive substances and addiction severity decreased significantly. An abstinence-oriented approach consisting of rapid detoxification followed by a combination of naltrexone and CRA is a clinically significant alternative for long-term methadone maintenance treatment for opioid dependent patients.

6.1. Introduction

An estimated 25,000 heroin dependent patients live in the Netherlands (16,000,000 inhabitants). About three-quarters are served by addiction treatment centres, particularly by means of methadone maintenance treatment. About 4,500 of the opioid dependent patients are involved in drug free treatment. Interventions directed at abstinence are regarded as problematic in terms of high drop-out and high relapse rates and prove to be effective only in a minority of motivated patients under stable living conditions with adequate social support (Van den Brink & Van Ree, 2003). Given the difficulty of achieving sustained abstinence (Amato et al., 2003), there is a tendency to focus on stabilisation and harm-minimisation (Krantz & Mehler, 2004).

Recent developments in the treatment of opioid dependent patients aiming at abstinence are promising. In general, detoxification in opioid dependent patients is not a substitute for treatment, but it is regarded as the first prominent component in a comprehensive treatment strategy (Kasser et al., 1997). Detoxification strategies based on antagonist-induced withdrawal seem to be associated with higher initial abstinence rates and with a guaranteed start of naltrexone maintenance treatment (Gowing, Ali & White, 2002a). Naltrexone blocks the euphoria induced by opioids and prevents the incentive property of sustained use. Studies on naltrexone maintenance show a clear effect in highly educated and socially well-integrated groups (Kirchmayer, Davoli & Verster, 2003). Pharmacotherapy of opioid addiction is more effective in combination with behavioral and psychosocial approaches (Kleber, 2003; Roozen, Kerkhof & Van den Brink, 2003), although innovative approaches to encourage medication adherence are needed (Weiss, 2004).

In the Community Reinforcement Approach (CRA) adherence to medication can explicitly be stimulated. CRA regards behavior as modifiable by positive reinforcement from the individual's real-life community context (Meyers & Smith, 1995). In general, there is evidence for the efficacy of CRA, with or without medication, in various substance-related disorders, including alcohol, cocaine and heroin (Roozen et al., 2004).

The objectives of this study were to determine whether such a comprehensive approach results in high, long-term abstinence rates after successful detoxification in opioid dependent patients and whether continuously abstinent patients do better than relapsing patients in other domains.

6.2. Methods

6.2.1. Study design and setting

From four addiction treatment centres in the Netherlands (Novadic, Jellinek, Parnassia and Kentron), 296 participants were recruited for this naturalistic study. Twenty-four did not meet the inclusion criteria (n = 5) or refused to participate (n = 19). After a standardized inpatient detoxification program of one-week (De Jong, Laheij & Krabbe, 2005) all 272 patients started treatment with naltrexone maintenance and CRA in an outpatient condition. Follow-up was conducted at 1, 10 and 16 months after detoxification.

6.2.2. Participants

All patients were recruited from the standard methadone maintenance programmes on a voluntary basis. They attended these programmes at least during the previous year, were at least 18 years old and met the diagnostic criteria for opioid dependence according to Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1994). They underwent several unsuccessful attempts to become abstinent, expressed their clear wish to become abstinent, and were familiar with the Dutch language. Exclusion criteria were: severe somatic diseases or psychiatric disorders, pregnancy, AIDS, doubts about the patient's willingness to co-operate and contraindications regarding general anaesthesia. Patients were not excluded because of dependence on other drugs or drug abuse. However, because of the unpredictable effects of

cocaine on the cardiovascular system during anaesthesia, treatment was postponed for 48 hours if a patient had used cocaine shortly before detoxification.

6.2.3. Treatment

The CRA protocol (Roozen et al., 2000) encompassed twenty-three sessions. Physicians and psychosocial therapists administered the sessions. This protocol was tailored on the CRA manual of Meyers and Smith (1995). In 13 sessions, a physician administered and monitored compliance with naltrexone (50-mg dd.), addictive behaviors, craving, and the occurrence of adverse events. Subjects had to be accompanied by a non-drug using coach during treatment as for example a partner, spouse or good friend, who specifically assisted the patient with taking naltrexone. Concurrently, in 10 psychosocial sessions, the lifestyle of the patient was assessed and discussed. In these sessions attention was paid to drug refusing behavior, relational issues, social counseling, recreational counseling, vocational counseling, problem solving abilities, training in social skills, and craving management.

6.2.4. Assessments

Independent research assistants assessed participants at baseline and during follow-up. The primary outcome measure was defined as self-report of no heroin and/or methadone use in the last 30 days verified by urine analysis for opioids at follow-up. The Cumulative Abstinence Duration (CAD) was defined as the period starting after detoxification until the first use of opioids. At baseline and at 16 months the European version of the Addiction Severity Index (Kokkevi & Hartgers, 1995) was used to assess the severity of seven areas of functioning: medical, employment, alcohol, substances, legal, family and social, and psychiatric. At all assessment points health domains were measured with the SF-36 (Ware & Sherbourne, 1992). The health related quality of life, based on societal preference values (index) and from the patient perspective (visual

analogue scale: VAS), was measured with the EuroQol-5D (Brooks, 1996). Use of other psychoactive substances and addiction severity was measured with the EuropASI and urine analyses. Craving was measured with a VAS and general psychopathology with the Symptom Checklist-90 (Derogatis, 1983).

Table 6.1. *Baseline characteristics of the 272 patients.*

	Mean baseline (SD)
Age (years)	35.9 (6.4)
Male (%)	82.0
Ethnic Dutch (%)	82.9
Fully employed (%)	50.2
Marital Status (%):	
Single	70
Married	14
Divorced/widow	16
Education (%):	
Lower	70.8
Secondary	20.4
Higher	8.8
Regular Drug use (years):	
Heroin	12.1 (5.9)
Methadone	7.4 (5.7)
Age at first heroin use	20.8 (5.1)
Age at first methadone use	24.1 (7.2)
Number of Previous detoxifications	7.9 (8.0)
EuropASI Severity scores (0-9):	
Physical Health	1.2 (1.5)
Work, education, income	2.2 (2.3)
Alcohol	.9 (1.7)
Drugs	6.2 (1.1)
Justice/police	1.6 (1.9)
Family/social relations	2.7 (1.8)
Psych/emotional problems	2.1 (1.9)
Gambling	.12 (.6)

Note: Figures are percentages, means and standard deviations.

6.2.5. Data management and statistical methods

An intention-to-treat analysis was performed. To test differences for continuous variables the general linear model with repeated measures was conducted on continuous variables with baseline levels as covariate. Missing data considering continuous variables were systematically replaced through analysis

provided by the expectation maximisation imputation algorithm. χ^2 tests were applied for dichotomous outcomes and the independent t-test for continuous outcomes. For all statistical analyses SPSS version 11.5 was used.

6.3. Results

After one, ten and sixteen-month follow-up, data were available for 78, 74 and 86% of the study population. Table 6.1 shows details of the patient population at inclusion. Participants attended an average of 6.6 sessions (SD = 3.8) from a physician and 4.3 (SD = 2.7) sessions of psychosocial CRA therapy.

Figure 6.1 shows the point prevalence of abstinence and the CAD slope. After one-month follow-up 46% of the patients were abstinent for opioids. After 10 and 16 months of follow-up the point prevalence was 28% and 32% respectively. The cumulative abstinence duration (CAD) shows a decline in abstinence rates. After 10 months 27% and after 16 months 24% were continuously abstinent.

Table 6.2 shows the changes over time for the secondary outcome measures.

Figure 6.1. *Point prevalence and cumulative abstinence duration (CAD) in opioid dependent patients at 1, 10 and 16 months post detoxification.*

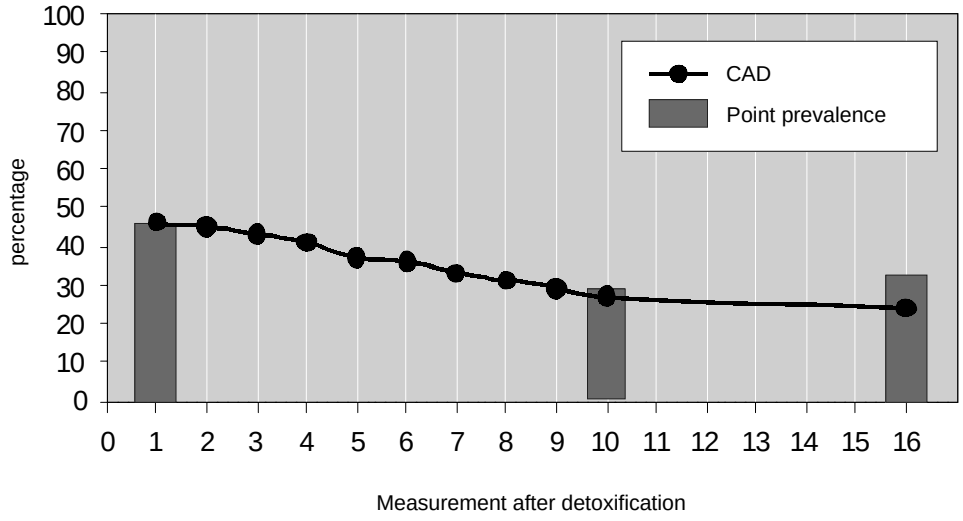

Table 6.2. *Secondary outcome measures in detoxified opioid dependent patients.*

	Baseline	Month 1	Month 10	Month 16
Health perception				
General health perception SF-36*	57.4 (20.1)	63.9 (22.0)	65.4 (22.0)	61.9 (22.8)
Quality of Life				
EuroQol Index (range 0 – 1)	.74 (.23)	.72 (.25)	.76 (.21)	.76 (.22)
EuroQol VAS (range 0 -100)	68.6 (17.7)	73.6 (18.6)	74.4 (18.3)	74.1 (18.7)
EuropASI Severity scores (range 0-9)				
Physical Health	1.2 (1.5)			1.0 (1.6)
Work, education, income	2.2 (2.3)			1.5 (2.1)
Alcohol	0.9 (1.7)			0.5 (1.3)
Drugs	6.2 (1.1)			3.0 (2.4)
Justice/police	1.6 (1.9)			.7 (1.6)
Family/social relations	2.7 (1.8)			1.1 (1.7)
Psych/emotional problems	2.1 (1.9)			1.7 (2.1)
Craving				
VAS	22.9 (26.5)	7.8 (16.8)	21.7 (30.6)	22.1 (30.1)
SCL-90				
Total score (range 90-450)	154.9 (49.5)	139.7(43.4)	140.2(50.3)	137.4(49.5)

*Note: Figures are means and standard deviations; *(range 0 – 100)*

There was a slight improvement in the general health perception of the SF-36 during the follow-up periods ($F = 9.67$, $P < 0.001$). The EuroQol-5D index showed a significant beneficial effect during follow-up ($F = 9.05$, $P < 0.001$). An overall improvement during follow-up was also observed for the EuroQol VAS ($F = 8.48$, $P < 0.001$). The ASI severity scores showed a significant improvement on all domains except for physical health (Table 6.2). With respect to craving, Table 6.2 shows a minor but statistically significant improvement on the VAS during the follow-up period ($F = 27.0$, $P < 0.001$). There was a difference between the VAS at intake and month 1 ($P < 0.001$). Mental health, as measured by the sum score of the SCL-90, showed a significant improvement over time ($F = 9.90$, $P < .001$).

All participants had declined in the number of substance-using days during the most recent 30 days, compared to baseline levels (Table 6.3). There were no significant differences in baseline characteristics between the continuously abstinent and the relapsing group. Table 6.4 shows the comparison of the secondary outcomes between abstinent and non-abstinent patients at 16-month follow-up. Compared with the non-abstinent patients the abstinent patients had a better health-related quality of life, lower severity scores on the EuropASI, except for the alcohol score, lower levels of craving and lower general psychopathology.

The opioid abstinent group used significantly less days cocaine (1.9 versus 6.3; P < 0.01) days) and benzodiazepines (3.6 versus 7.0; P < 0.01) compared with the relapsed patients.

Table 6.3. *Substances used in the past 30 days, according to ASI self-report.*

Substance	Baseline	Month 1	Month 10	Month 16	F	P
Alcohol	6.3 (10.3)	6.0 (8.1)	6.5 (9.1)	6.9 (9.4)	0.42	.74
Heroin	18.4[a] (12.1)	3.0[b] (7.5)	8.3[c] (12.0)	10.3[c] (13.0)	53.88	.00
Methadone	22.9[a] (11.0)	2.9[b] (8.1)	8.2[c] (12.5)	10.6[c] (13.4)	75.73	.00
Opiates (other)	0.1 (1.7)	0.1 (.4)	0.4 (3.1)	0.3 (2.1)	0.79	.50
Medicines	6.0 (11.1)	8.4[a] (11.7)	5.2[b] (10.1)	5.7[b] (10.7)	4.40	.01
Cocaine	4.1 (7.4)	2.3 (5.8)	3.5 (7.7)	4.53 (8.8)	0.83	.48
Amphetamines	.1 (.4)	.0 (.2)	.0 (.2)	.0 (.0)	1.72	.16
Cannabis	7.5 (11.6)	6.8 (1.6)	7.8 (11.7)	8.5 (12.4)	0.65	.58
>> 1 substance	18.1[a] (11.9)	4.9[b] (9.0)	8.7[b] (13.2)	10.7[b] (12.6)	39.26	.00

Note: Figures are means and standard deviations. Means with different superscripts differ in pair-wise comparisons (SIDAK) at P < 0. 05.

Table 6.4. *Comparison of secondary outcome measures between abstinent and non-abstinent patients at 16-month follow-up.*

	Abstinent	Non-abstinent	P
Health perception			
General health perception SF-36 (range 0 – 100)	71.8 (21.2)	55.5 (21.5)	.030
Quality of Life			
EuroQol Index (range 0 – 1)	.84 (.17)	.74 (.23)	.010
EuroQol VAS (range 0 -100)	81.6 (15.4)	68.9 (19.2)	.013
EuropASI Severity scores (range 0-9)			
Physical Health	.8 (1.5)	1.2 (1.6)	.06
Work, education, income	.8 (1.5)	2.0 (2.4)	< .001
Alcohol	.5 (1.2)	.06 (1.3)	.46
Drugs	.7 (1.3)	4.5 (1.7)	<. 001
Justice/police	.5 (1.3)	.8 (1.8)	.07
Family/social relations	.7 (1.2)	1.4 (1.8)	<. 001
Psych/emotional problems	1.1 (2.0)	2.1 (2.3)	.001

Note: Figures are means and standard deviations.

6.4. Discussion

This study explored the long-term outcome of opioid antagonist induced withdrawal in opioid dependent patients, followed by a comprehensive treatment,

in which naltrexone maintenance was combined with the Community Reinforcement Approach. Twenty-four percent of participants were persistently abstinent over a 16 months follow-up period.

These positive results can be attributed to the use of the opioid antagonist precipitated withdrawal techniques, which facilitate the likelihood of successful induction into maintenance naltrexone treatment (Gerra et al., 2000; McGregor et al., 2002). The results are in line with the contemporary literature that demonstrates the value of integrating pharmacological agents and cognitive behavioral oriented therapies that have been widely promulgated to achieve and maintain long-term abstinence in opioid abuse or prevent relapse (Carroll et al., 2001; Roozen, Kerkhof & Van den Brink, 2003; Weiss, 2004).

The degree of success is much higher than that which could be expected from regular treatment approaches, such as methadone tapering (Amato et al., 2003). Most studies have reported upon follow-up periods ranging from one week to one month (O'Connor & Kosten, 1998). More recent reviews suggest that it may not be possible to draw conclusions concerning the long-term effectiveness or cost-effectiveness of withdrawal induced by opioid antagonists with minimal or heavy sedation or anaesthesia (Gowing, Ali & White, 2002a,b). Several recent studies report on long-term outcome, yielding (continuous) abstinence rates ranging from 13 to 80% (Albanese et al., 2000; Bochud Tornay et al., 2003; Cucchia et al., 1998; Hensel & Kox, 2000; Lawenthal, 2000; Rabinowitz et al., 1997, 1998 and 2002). It is impossible to draw general conclusions from these reports because of the wide variation in study design, objectives, data assessment, sample size, variety in populations and treatment modalities. Naltrexone may be an efficacious adjuvant in the therapy. This is especially so for (highly) motivated patients who fear the severe consequences of not stopping taking opioids. Such patients may include health-care professionals who may be dismissed or parolees who may be returned to prison (Kirchmayer et al., 2003). The population in this study comprised a regular group of patients in a methadone maintenance programme who were mostly single, and had a low educational level and a fifty percent unemployment rate. These characteristics contrast with the aforementioned beneficial effects only for selected groups of opioid dependent patients.

Considering their low level of social, psychological and physical problems the study group could be considered a more hopeful category of methadone maintenance patients. It is noteworthy that abstinence was associated with an improvement in health. Those who did not relapse showed improvements in addictive behaviors, craving, health, and health-related quality of life. Even those who were only temporarily abstinent showed improvement on these outcomes.
No differences in baseline characteristics were found between the group who remained abstinent for 16 months and those who relapsed. No significant predictors for continued abstinence were found among the large number of characteristics included in the study. Consequently, abstinence as a goal of treatment is attainable for a larger proportion of opioid dependent patients than has been assumed to date. We would conclude that all patients who are motivated for an abstinence-oriented approach would be suitable for the comprehensive series of interventions described in this paper.

The design chosen for the add-on effect of general anaesthesia in rapid induction of withdrawal was that of a randomised controlled trial. Because no differences were found between the two treatment groups, they were aggregated. This resulted in a naturalistic design with a non-randomised evaluation as major limitation, even though it was performed following recent guidelines for such studies (Caetano, 2004). The study aimed to follow detoxified opioid dependent patients over a follow-up period of 16 months. This meant that no conclusions could be drawn concerning the causal relationship between the combination of naltrexone and CRA and abstinence in opioid dependent patients nor for the differential effect of CRA or naltrexone.

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Acknowledgements:

We would like to thank the following individuals who participated in the study:
Katinka F.M. Damen, Renate F.M. Elferink, Katinka M. van der Heiden, Petra J.A. van der Kroft, Annet Ruijsink, Cor A.G. Verbrugge, Marrïete W. van Westen, Gemma van de Wouw [research assistants]
Wim van den Brink, Peter J. Geerlings, Vincent M. Hendriks, Jan-Pieter Vorsteveld [coordination staff]
Jaco P. Duret, Paul P.M. Maas (Ignatius Ziekenhuis, Breda); Victory R.M.V. van Cauter, Peter F.J. Baaijens, Hans F. van de Zee (Ziekenhuis Bernhoven, Veghel); Karol Jacz, Hans S. Pöll (Medisch Centrum Haaglanden Westeinde, 's Gravenhage); Robert Sie (Rijnland Ziekenhuis, Leiderdorp) [anesthesiologists]
Jenneke Weijers (Jellinek Laboratory), Rob W. Kempen (Ziekenhuis Apotheek Laboratorium Venray) [urine analysis]

CHAPTER 7

Effects on smoking cessation: naltrexone combined with a cognitive behavioral treatment based on the Community Reinforcement Approach

Abstract

A promising option in substance abuse treatment is the Community Reinforcement Approach (CRA). The opioid antagonist naltrexone (NTX) may work in combination with nicotine replacement therapy (NRT) to block the effects of smoking stimuli in abstinent smokers. Effects of lower doses than 50 mg/dd. have not been reported. A study was conducted in Amsterdam in 2000/2001 with the objective to explore the effects of the combination NTX (25/50-mg dd.), NRT, and CRA in terms of craving and abstinence. In a randomized open label, 2 x 2 between subjects design, 25 recovered spontaneous pneumothorax (SP) participants received 8 weeks of treatment. Due to side effects, only 3 participants were compliant in the 50mg NTX condition. Craving significantly declined between each measurement and there was a significant interaction between decline in craving and craving measured at baseline. The abstinence rate in the CRA group was nearly double than in the non-therapy group (46% versus 25%; NS) at three months follow-up after treatment.

7.1. Introduction

Naltrexone (NTX), which is traditionally used to prevent alcohol and opioid abuse, recently emerged in the tobacco literature (e.g. Krishnan-Sarin, Meandzija, & O'Malley, 2003). It is suggested that there may be a link between opiates and nicotine (Krishnan-Sarin, Rosen & O'Malley, 1999). Under controlled laboratory conditions, where habitual smokers smoked cigarettes, an increase in beta-endorphin levels co-occurred with increases in plasma nicotine concentrations (Pomerleau et al., 1983). It is conceivable that nicotine stimulates endogenous opioid release, which provides positive reinforcement for smoking.

Subsequently, an opioid antagonist, such as NTX, may (partially) block these rewarding effects. In a study of Sutherland et al. (1995), it was suggested that NTX reduced the perceived difficulty of abstaining during 24-h cigarette withdrawal. Some additional support for the use of NTX came from a study of King & Meyer (2000) who demonstrated that NTX in controlled conditions significantly reduced the total number of cigarettes smoked. In a study conducted by Wewers et al. (1998) it was demonstrated that plasma nicotine levels, number of cigarettes smoked daily and self reported satisfaction with smoking were significantly lower among those treated with NTX.

A review of David et al. (2002), however, shows that short-term trials of NTX yield conflicting results with regard to effects on ad libitum smoking, withdrawal symptoms, mood states, subjective and physiological responses to smoking. In addition, several placebo-controlled studies ascertained no support for NTX on a variety of biochemical and behavioral measures of nicotine intake or even produced negative effects on mood (e.g. Brauer et al., 1999; Wong et al., 1999; Sutherland, 1995). Thus at best it remains unclear whether NTX helps smokers quit (David et al., 2002).

However, as to our knowledge, all NTX studies on smoking cessation examined the effects of the 50-mg daily dose. Only one study could be identified by using 100-mg dd. of NTX (Sutherland et al., 1995). This study demonstrated no dose response effect between 50 and 100 mg NTX per day (Sutherland et al., 1995) and no other studies could be identified with lower dosages.

In a review, Silagy et al. (2002) concluded that all forms of Nicotine Replacement Therapy (NRT) are effective as part of a strategy to promote smoking cessation. Consequently, it has been demonstrated that the concurrent use of NTX and NRT is beneficial for smoking cessation (Hutchison et al., 1999; Krishnan-Sarin, Meandzija, & O'Malley, 2003), for instance because it may ameliorate withdrawal symptoms, dysphoria and sedation (Hutchison et al., 1999). Additionally, it is suggested that NTX augments the efficacy of NRT in terms of craving (Hutchison et al., 1999; Krishnan-Sarin, Meandzija, & O'Malley, 2003). Also the single use of NTX may reduce craving (Houtsmuller et al., 1997; King & Meyer, 2000). Craving is thought to play an important role in maintaining regular smoking patterns in smokers, and in leading to relapse in smokers attempting to quit (Houtsmuller & Stitzer, 1999). Although still ill understood, craving mostly is referred to as a compulsory desire to use (c.f. Robinson & Berridge, 1993, 2001). In addition, craving is considered as a complex, dynamic, multi-dimensional phenomenon (Barabási, 2003; Buscema, 1998), consisting of biological, psychological and social components.

With respect to psychosocial treatments, the Community Reinforcement Approach (CRA) is a promising option, which ascertained evidence in favor of CRA in the alcohol-, cocaine- and opioid treatment (Roozen et al., 2004). CRA has also been mentioned in relation to smoking cessation (Poldrugo et al., 2002). CRA is a comprehensive cognitive behavioral oriented treatment package that focuses on environment (community)-organism interactions to rearrange a substance abusing lifestyle (Meyers & Smith, 1995). It is based on the view that substance-related reinforcers and the relative lack of alternative reinforcers unrelated to substance abuse maintain dependence. Development of alternative rewarding activities that are incompatible with substance use is essential to initiate and maintain abstinence (Schottenfeld, et al., 2000). CRA integrates concomitant administration of pharmacological agents with psychosocial aspects.

It seems likely that CRA, as a novel multi faceted approach, is appropriate to foster abstinence in a smoking cessation therapy. In the present study this expectation was addressed. The objective of this study was to explore (1) the effects of CRA in terms of abstinence, therapy retention and treatment

satisfaction and (2) a dose response effect of NTX in terms of craving and abstinence.

7.2. Method

7.2.1. Participants

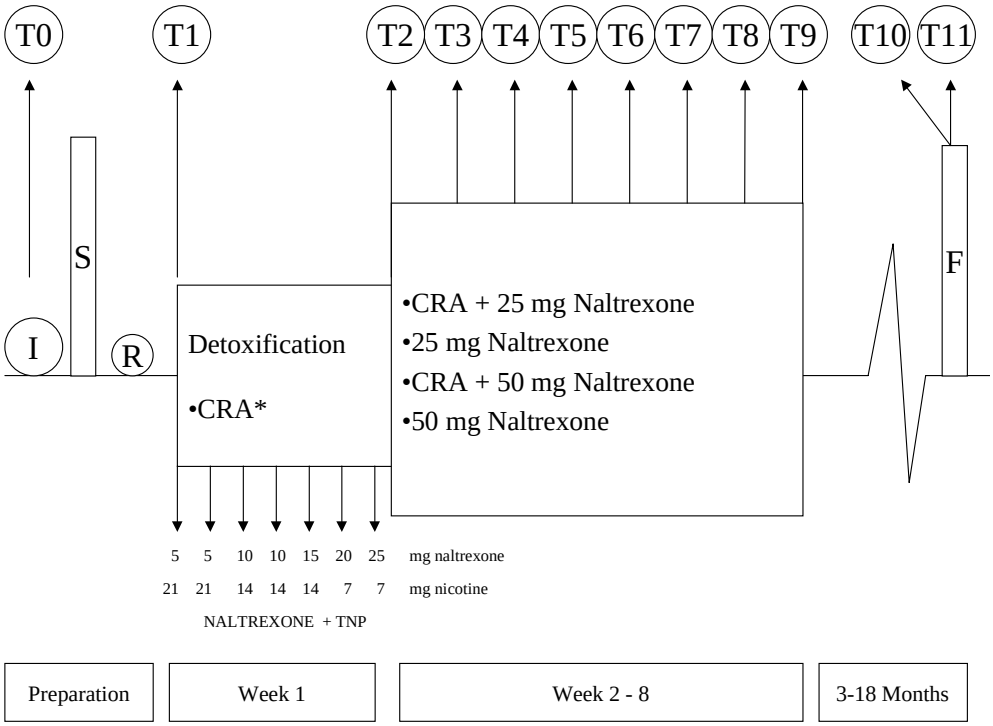
Twenty-five participants were recruited from a database of 181 recovered spontaneous pneumothorax (SP) patients treated at the VU medical center (22 participants) and Slotervaart hospital (3 participants) in Amsterdam, the Netherlands. SP is considered as a smoking related disease, because tobacco use enhances the chance of having peripheral airway inflammation (Snider, 1992), which has a role in the pathogenesis of idiopathic SP (Schramel et al., 1997; Smit, 1999). The chances of contracting SP is 8-22 fold higher when people smoke (Bense, 1987) and smoking cessation reduces this chance (Sadikot et al., 1997). All participants were contacted by telephone to enquire if they wanted to participate. Participants were included if they were between the ages of 18 and 65, smoked at least 15 cigarettes daily for a minimum of five years, and expressed the wish to stop smoking. Participants should have performed at least three unsuccessful attempts to stop smoking in the past five years. They should not simultaneously participate in another smoking cessation treatment and they should have the collaboration of a non-smoking concerned significant other to assist the participant in his attempt to stop smoking. Participants were excluded if they were dependent on opioids, cannabis or alcohol. All participants gave written informed consent.

7.2.2. Procedure

The treatment (T1-T9) was provided for eight weeks (Figure 7.1). Prior to the treatment, participants and their significant other (e.g. supportive partner or friend) were invited for an information visit (T0) to collect socio-demographic, medical history data (Table 7.1), and to explain the rationale and procedure. Participants

were consecutively randomized by a using a block design and allocated to four treatment groups (Figure 7.1).

Figure 7.1. *Treatment plan and flowchart of the visits (T0 to T10).*



*Note: T10 and T11 are follow-up contacts. T11 was only a telephone contact. I = Intake, S = Selection, R = Randomization and F = Follow-up. The detoxification encompassed a gradual increase of NTX from 5 mg (day 1 & 2), 10 mg (day 3 & 4), 15 mg (day 5), 20 mg (day 6) to 25 mg (day 7). The NRT administration was tapered down by applying 21 mg/24h (day 1& 2), 14 mg/24 h (day 2 – 5) and 7 mg/ 24 h (day 6 & 7). For particpants allocated to both 50-mg NTX conditions, NTX was further increased from 25 mg to 50 mg at T2. * Only for participants allocated to the CRA condition.*

In the week following the first treatment visit (T1) the administration of NTX (Antaxone®), which was administered in oral solution, was gradually increased from 5 mg up to 25 mg. NRT (Nicotinell®) was tapered from 21 mg/24h to 7 mg/ 24 h (see Figure 7.1). The rationale for this non-standard use of the NRT taper procedure was to ameliorate possible withdrawal symptoms and to reduce possible side effects of the NTX induction. At T2 the NTX dosages were in

alignment with the randomization procedure: 25 mg NTX, 25 mg NTX + CRA therapy, 50 mg NTX and 50 mg NTX + CRA therapy. The timing of the clinical and laboratory assessments is summarized in Table 7.2. At the weekly visits, data was collected and the NTX was administered (HJW/SvB). The participants allocated to the CRA condition received concomitant CRA treatment at visit 1, 2, 3, 5 and 7. The non-treatment group received no additional treatment. Each participant was seen at the same time of day at all visits. A follow-up took place 3 months after the treatment visits, and a second follow-up was conducted 1½ year later by telephone to assess continuous abstinence. Only participants who had been abstinent at 3 months were contacted for second follow-up. Dropouts were considered as smokers.

CRA

The cognitive behavioral treatment was based on CRA (Meyers & Smith, 1995) to give support during smoking cessation, and is protocol driven (Roozen & Kerkhof, 2000). Masters-level psychology students conducted this therapy, which took 5 sessions. Treatment integrity was guided by a three days training course and weekly individual supervision (HGR). Sessions were focused on motivation, adherence with treatment and NTX administration, skill training, functional analysis, and on creating a monitoring system. The 'Stimulus Control' procedure (Azrin et al., 1994) was employed to eliminate high-risk social situations that are precursors to smoking, and, to increase the amount of time spent engaging in smoking-incompatible activities.

Objective and subjective measures

An overview of the measures used is provided in Table 7.3. The success of cessation is measured by abstinence according to self-report. Of the collected urine samples, the cotinine values were analyzed to verify self-reported smoking status.

Table 7.1. *Sample characteristics at baseline*

Variable	25mg	25mg & CRA	50mg	50mg & CRA	TOTAL	P
No. of cases	6	6	6	7	25	NS
% Male	50	83	67	86	72	NS
% Married/living together	50	50	33	86	56	NS
% Min. secondary education	83	100	100	83	92	NS
Age	39.83(4.99)	41.00(3.7)	43.67(6.06)	46.43(3.98)	42.88(2.27)	NS
No. cigs/day daily	21.83(2.99)	21.67(2.11)	25.60(2.11)	20.29(1.97)	22.13(1.34)	NS
No. of quitting attempts	2.16(0.87)	2.67(0.67)	1.40(0.60)	2.17(0.52)	2.29(0.33)	NS
Score on perceived health status	7.80 (0.84)	7.33 (0.52)	7.80 (0.84)	6.86 (1.21)	7.39 (0.94)	NS
Years recovered from SP	8.83(3.21)	12.33(3.49)	8.50(2.90)	5.57(2.22)	8.70(1.50)	NS
SCL-90 score	120.17(6.12)	114.00(7.44)	126.00(5.91)	135.57(18.55)	124.40(5.76)	NS
No. of concerned others	8.00(4.04)	5.83(1.96)	6.50(1.28)	5.00(1.17)	6.28(1.11)	NS
Alcohol units/day	1.33(0.49)	1.33(0.42)	2.20(0.92)	2.14(0.77)	1.75(0.32)	NS

Note: The type of socio-demographic areas covered items such as age, sex, education level, marital status, and number of concerned others. A visual analogue scale (VAS) ranging from 1 (poor health) to 10 (excellent health) assessed the perceived (subjective) health status. Displayed are numbers, percentages, mean scores, standard deviation and significant-levels (P < 0. 05).

Table 7.2. *Flow chart of study assessments points of clinical measures/ intervention.*

	T0	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11
Time (hour)*	1.5	1.0	0.5	0.25	0.5	0.25	0.25	0.25	0.25	1.5	0.5	0.1
Soc.Demogr. data	♦											
VAS health status	♦											
Physical examination	♦											
Urine sample	♦	♦			♦					♦	♦	
Self-report smoking	♦	♦			♦					♦	♦	♦
VAS (craving)	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	
VAS (taste)	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	
VAS (CRA)										♦		
CSQ-8										♦		
SCL-90	♦									♦		
CRA**		♦	♦	♦		♦		♦				

*Note: * Average time needed to assess data, administer medication, provide instruction and information and advice, document side effects, etc. ** Only for participants allocated to the CRA condition. Each CRA treatment session lasted about 60 minutes.*

Design and statistical analysis

A 2x2 factorial between-subjects design was utilized. The significance level was set at P< 0.05.

Table 7.3. *Objective and subjective measures.*

Objective measure	*Instrument*	*Objective*	*Number of items*	*Average time (min)*	*Type*	*Additional information*
	Urine collection	Cotinine, a primary metabolite of nicotine with a half-life of 15-20 hours, has been used as a biomarker to uncover those who continue to smoke and confirmation of cessation in treatment studies (Lee et al., 1993; Bergen, 1999).		10	The samples were analyzed in the clinical chemical laboratory of the VU Hospital with the Proclaim Cotinin Enzymimmunoassay kit (Rolf Greiner Biochemical, Kat.-Nr.: 18251 and calibrator kit Kat.-Nr.: 150404) on an ELAN-Analyzer (Merck). The intra- and interassay percent CV for cotinine were 8.5 and 9.3 respectively.	The limit of detection of this method is 40 ng/ml of cotinine. Up to 120 ng/ml of cotinine was considered as none or passive smoking, above this level was considered as evidence of smoking*. The cut-off levels were determined on base of a sample of smoking and non-smoking participants in a validation research.
Subjective measure	*Instrument*	*Objective*	*Number of items*	*Average time (min)*	*Type / Instruction*	*Additional information*
	VAS (Craving)	Measures the subjective state of craving	1	1	The 100 mm line, ranging from “not at all” to “extremely”, was accompanied by the instruction: “Please put a mark on the line which represents best your urge to smoke”.	
	VAS (Taste)	Measures the taste of the cigarette if the participant had smoked	1	1	The 100 mm line ranged from “good” to “bad”, and was accompanied by the instruction: “If you have smoked, please put a mark on the line how the cigarette tasted”.	
	SCL-90	Designed to detect nine major dimensions of psychopathology including anxiety, agoraphobia, depression, somatization, insufficiency, interpersonal sensitivity, hostility, insomnia, and psychoticism.	90	20	Self-report	The theoretical factor structure of the SCL-90 was validated by confirmatory and exploratory factor analyses of ratings from a heterogeneous sample of psychiatric outpatients (Derogatis & Cleary, 1977). The grand mean of all 90 items primarily indicate general psychiatric distress, which may provide information consistent with the empirical factor structure of the SCL-90 (Zack, Toneatto & Streiner, 1998).
	CSQ-8	The CSQ-8 consists of eight four-point questions, to measure global satisfaction.	8	5	Self-report	The CSQ-8 has been used in a variety of treatment settings. The questionnaire has been frequently recommended as a reliable measure of global satisfaction (Larsen, et al., 1979).
	VAS (CRA)	Measures satisfaction with the contents and method of the CRA therapy	1	1	The 100 mm line ranged from “good” to “bad”, and was accompanied by the instruction: “Pease put a mark on the line how satisfied you are with the CRA treatment”.	

*Note: *Data covering the cotinine values were categorized in three groups: up to 120 ng/ml of cotinine was considered as none or passive smoking, 120-1600 ng/ml of cotinine was considered as smoking less than 10 cigarettes daily, 1600-2000 ng/ml of cotinine was regarded as smoking more than 10 and less than 20 cigarettes daily. Over 2000 ng/ml was considered as more than 20 cigarettes daily smoked.*

Table 7.4. *Scores on the SCL-90 at baseline and at the end of treatment.*

	Baseline	End of treatment	P
Subscale	(*n*=14)	(*n*=14)	
Anxiety	12.79 (2.29)	11.93 (1.94)	NS
Agoraphobia	8.00 (1.24)	7.57 (0.94)	NS
Depression	21.43 (3.90)	20.07 (3.97)	<. 05
Som. complaints	16.43 (2.88)	15.50 (3.08)	NS
Insufficiency	12.43 (2.71)	12.07 (2.73)	NS
Sensitivity	22.79 (3.87)	22.29 (5.31)	NS
Hostility	6.86 (.77)	6.79 (.80)	NS
Insomnia	5.21 (1.67)	4.79 (1.81)	NS
Psychotism	11.07 (1.86)	10.50 (1.51)	NS
Psneur	117.00 (15.61)	111.50 (16.68)	NS

Note: Displayed are numbers, mean scores, standard deviations and significant-levels (P < 0. 05) for subscales and total score (Psneur) of the SCL-90.

Descriptive statistics, paired sample T-test, Spearman's rho and one-way ANOVA's were used to compare sample characteristics. Logit analyses were conducted to analyze main effects or significant interactions between the 4 conditions. A General Linear Model (GLM) repeated measures analyses was conducted, with as between-subjects factors the NTX doses (25 mg versus 50 mg) and CRA therapy (therapy versus none), and as the within-subjects factor the 10 VAS measurements. The baseline VAS was used as covariate. Missing data analysis, considering the VAS, was conducted by the expectation maximization (EM)-algorithm. After this, a t-test was used to analyze if the craving reduced linearly or remained constant. The tests of the within subjects effects were analyzed using the univariate approach with Huynh-Feldt correction.

7.3. Results

7.3.1. General outcomes

Sociodemographic characteristics, scores on the SCL-90 and alcohol use were not statistically different between the four groups at baseline (Table 7.1).

The scores on the SCL-90 at baseline and at the end of treatment did not differ significantly, except for a decrease in depression (P = 0.026, Cohen's d = 0.35; Table 7.4). One week of nicotine replacement was sufficient to ameliorate withdrawal symptoms, but participants preferred a longer use of NRT. Eight participants withdrew from the treatment because of self-reported side effects induced by NTX (2) or because of relapse (6). The overall dropout was 32%.

In general, most participants tolerated NTX well, but 73% found the taste of the NTX fluid unpleasant. The 50-mg doses NTX-treated participants (13) experienced more side effects compared to the 25-mg doses NTX-treated participants. Reported side effects were headache, dizziness, nausea, insomnia, sleepiness and decrease of taste. Due to this, in the 50 mg NTX condition, five participants halved this dose to 25 mg. Three participants refused to continue with NTX because of side effects. As previously reported two participants allocated to the 50-mg condition dropped-out. This left only 3 participants to be compliant in the 50-mg condition. In contrast, only one participant allocated to the 25-mg condition decreased the daily dose NTX to 12.5 mg. An intention to treat analysis showed no significant difference between the NTX conditions. As a result, the two NTX conditions were collapsed.

7.3.2. Treatment attendance, satisfaction and evaluation

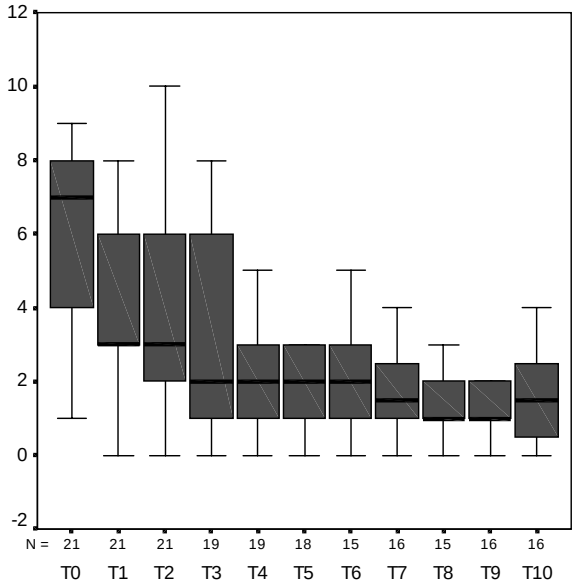
CRA participants did attend a mean number of 4.5 (SD = 1.2, range = 1-5) sessions. Participants who received CRA were, in general, satisfied with the contents and method of the CRA therapy (Mean = 7.3, SD = 0.90, range = 6.0 - 9.3). The satisfaction about the received treatment in general, measured with the CSQ-8, was high (Mean = 25.8, SD = 4.0, range = 22-32).

7.3.3. Abstinence and treatment

The correlation between self-report daily smoked cigarettes and the cotinine values (T0, T1, T4, T9, and T10) is 0.68 (P < 0.01), with respect to three

categories of smokers (Table 7.3). When the categories were collapsed into the dichotomous measure abstinent or smoking, the correlation between the cotinine values and self-report is perfect (1.00, P < 0.01). At 3 months after the end of treatment (T10) the abstinence rate in the CRA group was higher than in the non-therapy group (46% versus 25%) but this did not differ significantly. At 1½-year follow-up (T11), participants were asked by telephone: ”Do you smoke?” Hundred percent of the participants gave a self-report. The smoking abstinence rate for the non-CRA condition was 17%. In the CRA therapy group the abstinence rate was 31% (NS). The overall abstinence rate after 1½ year was 24%. Sixty-seven percent of the participants who where abstinent after 3 months remained abstinent thereafter.

Figure 7. 2. *Box plot representing the craving (VAS) distribution (T0-T10).*



Note: Outliers and extremes are suppressed. Black line in the box represents the median value. Horizontal lines under and above the box (whiskers) indicate the range of values (excluding outliers and extremes). Lenght of box indicates the interquartile range (IQR), which covers the range between 25th and 75th quartile. The IQR is an estimate of the spread of the data.

7.3.4. Craving outcomes

Craving significantly declined each weekly measurement with a regression coefficient of 0.28 points (SD = 0.24) on the VAS scale of 0 – 10 (t = 5.3, d*f* 20, P < 0.001; Figure 7.2). There is a significant interaction (F = 2.47, d*f* 6.5 and 104.2, P =

0.025) between the sequential time points and baseline craving. The interaction effect indicates that the higher the participants' baseline craving, the stronger the decrease in craving. The correlation between baseline level of craving and the slope of craving is -0.53 (P = 0.014). The VAS measures pertaining to the taste of the cigarette, if the participant had smoked, showed neither interaction effects nor a significant trend.

7.4. Discussion

This study yielded a high agreement between biochemical cotinine values and self-reported tobacco consumption. Consequently, the abstinence rates can be considered as valid. An effect of CRA therapy is suggested with nearly double the amount of abstinence. However, the difference is not statistically significant. This lack of a significant effect may be due to the small study sample. To calculate the number of participants we would have needed to find a statistically significant effect, we merged the data (proportions of abstinence at 3 months; 25% versus 46%, power .8 and alpha .05) in an Arcsin formula (Lemeshow et al., 1990; Lwanga & Lemeshow, 1991). This resulted in 63 participants in each group (one-sided). Another reason concerns the relatively large amount of time consumed to collect data, provide information and give instructions by a researcher. This considerable amount of attention may have diluted the CRA effect.

Due to side effects, a comparison between the 25 mg and the 50 mg NTX doses was not meaningful. Non-compliance with regard to dosis contaminated the conditions, which impaired the randomization procedure. More than 50 percent of the participants in the 50-mg NTX condition reduced the doses to 25 mg or to none. Participants were generally satisfied with the treatment in general, and NTX, but still suffered side effects, even with 25-mg doses. Side effects after NTX induction have also previously been reported (e.g. Sutherland et al., 1995; Brauer et al., 1999). However, the severity of the side effect has not caused such a high non-compliance in a 50-mg condition in previous studies. Seventy three percent of the participants rated the taste of the NTX oral solution (10-ml) as unpleasant,

which might have been caused by relative large doses of concomitant additives such as saccharine (1 mg) and sorbitol (70%).

There was a significant decline in craving and a significant interaction between baseline craving and decline in craving. Methodological limitations preclude us drawing firm conclusions regarding the effect of NTX on craving. But the findings do suggest that additional research on NTX related to craving is warranted, as analogue results previously have been reported (King & Meyer, 2000).

The protocol driven cognitive behavioral treatment program based on CRA is rather extensive in comparison to many regular smoking cessation programs (especially self-help), which could compromise participants' satisfaction. Results indicate, however, that participants were satisfied with the CRA program and found the frequency and the duration of the treatment appropriate.

With regard to methodological limitations, non-blinding of the conditions, small sample size, and the necessity for collapsing the two NTX dose conditions, we were limited to ascertain an effect between 25 mg and 50 mg NTX condition. Further double blind, (placebo) controlled, research in a larger population is needed to establish the effects of a low dose of NTX and/or NRT on smoking behavior. We recommend in further research the administration of NTX in pill form. CRA constitutes an innovative approach in smoking cessation treatment. The results in this study support the call for further research.

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Acknowledgements

Part of this article was based on the undergraduate honors thesis of S.E.C. van Beers, supervised by H.G. Roozen & A.J.F.M. Kerkhof. We thank E. Blaauw, W. van den Brink, L. DeFuentes-Merillas, F. Loen, J. Nijhof, and P. van Spiegel for their assistance and comments on an earlier draft. Special thanks to P. Dekker for his advice and assistance regarding the statistical analyses. We would also thank N. Loevy, L. de Wit, T. Nijdam, T. van der Lee, J. Schippers, J. Boersma, L.

Rozemeyer & L. Scheffer for providing cognitive behavioral therapy based on CRA. Zambon primarily sponsored this study. We also thank STIVORO - for a smoke free future, and Novartis, for additional funding and support. Naltrexone (Antaxone®) was provided in oral vials by Zambon, Amersfoort, the Netherlands. Nicotine patches (Nicotinell®) were provided by Novartis, Breda, the Netherlands. These agencies had no role in the conduct, interpretation, or analysis of the study. The Medical Ethical Committee of the Vrije Universiteit hospital approved this study.

CHAPTER 8

General Discussion

8. General Discussion

In this dissertation reviews and empirical studies were presented about the effectiveness of the Community Reinforcement Approach (CRA), the prescription of naltrexone (NTX), and the combination of both interventions for patients with substance use disorders. Furthermore, guided by a literature search, CRA protocols were unfolded to assess the differences and similarities with regard to intervention components. These studies enable conclusions and recommendations and generate topics for future research.

8.1. CRA and NTX in substance use disorders

This thesis focused on CRA combined with NTX in patients with substance use disorders. According to the expectations:

1. The CRA review and additional empirical research on this topic asserted that CRA is an effective treatment to manage substance use disorders including alcohol, cocaine, tobacco and opioid.
2. NTX is an effective agent under the condition that patients are compliant in the treatment of alcohol and opioid use disorders. The problem of early drop-out and non-compliance suppresses NTX' effectiveness in normal clinical practice.
3. Combinations of the various CRA components and pharmacotherapy contribute to successful outcome in the treatment of substance use disorders. These components enable subjects to sample rewarding activities in their natural environment that are incompatible with, or a valued replacement, of substance use.

8.1.1. Discussion of the effectiveness of CRA

An important research question was whether CRA is effective in the treatment of patients with alcohol, opioid, tobacco and cocaine use disorders. This topic was addressed by a review of the literature (*Chapter three*) and by collecting new empirical data (*Chapters five, six, and seven*).

The alcohol studies included in the review yield strong evidence that CRA, without additional therapies, is more effective than usual care in terms of reducing the number of drinking days. There is conflicting evidence with regard to continuous abstinence as the criterion. In addition, there is moderate evidence that CRA in combination with disulfiram is more effective than usual care with disulfiram in terms of reducing the number of drinking days.

No difference was found in the review between CRA with disulfiram and usual care with disulfiram in terms of continuous abstinence, although the evidence is limited. It should be noted that CRA is not focused on abstinence per se: CRA identifies and implements positive reinforcers that could perform as incentives to change maladaptive behaviors. In addiction treatment, CRA addresses self-management to regulate alcohol drinking when it occurs.

The reviewed studies of cocaine dependence provided strong evidence in favor of ‘CRA with incentives’ compared to usual care, with regard to cocaine abstinence. In addition, the meta-analysis convincingly demonstrated that CRA with abstinence-contingent 'incentives’ is more effective than single CRA (non-contingent incentive) treatment aimed at cocaine abstinence.

The few studies in opioid dependent patients provided limited evidence for the effectiveness of ‘CRA with incentives’ compared to usual care in a detoxification program. There is also limited evidence that single CRA is more effective than usual care in a methadone maintenance program. Subsequently, empirical research was conducted on CRA combined with NTX in the treatment of opioid-dependence (*Chapter five and six*). These studies yielded positive results in terms of illicit drug use reduction and general health. A relative large subgroup of opioid dependent patients was able to achieve sustained abstinence. In this respect

abstinence appears to be a feasible goal, and remains an important option next to long-term methadone maintenance in the management of opioid dependence.

Research on smoking cessation yielded a positive effect of CRA therapy, with CRA therapy having nearly double the number of participants maintaining abstinence compared to the NTX alone condition (*Chapter seven*). However, the difference was not statistically significant. A viable reason for this finding may be the small sample size, as CRA appears to constitute an innovative approach in smoking cessation treatment.

These findings corroborate previously conducted meta-analyses on CRA (Finney & Monahan, 1996; Holder et al., 1991; Miller et al., 1995, 1998 and 2003; Miller & Wilbourne, 2002). “The outcomes achieved with CRA equal or exceed the results of any controlled treatment-outcome study in the alcohol literature” (Stitzer & Higgins, 1995, p. 1815). In general, as shown by the review (*Chapter three*), CRA is an effective treatment modality and is more effective than most usual treatments.

Therefore, it is recommended to implement CRA in general outpatient routine practice. In contrast, there is insufficient evidence for the added value of inpatient treatment modalities when compared to outpatient care (Miller et al., 1998 p. 213). The outcomes following inpatient treatment are strongly related to the extent of participation in outpatient aftercare (Miller, 1997). Therefore inpatient programs should be geared to pragmatic needs such as treating intoxication, detoxification, medical co-morbidity, suicide threats, elevated levels of psychiatric symptoms etc. Patients with an absent social network or without housing may also temporarily benefit from inpatient treatment that aims on (synthetic) network development. But this need does not preclude the outpatient focus of CRA. In this respect Miller (1997) suggests that the crucial treatment is the one that occurs while the subject is in the natural environment (Miller, 1997, p. 499).

8.1.2. Discussion of the effectiveness of NTX

The μ-subtype opioid receptor signaling is activated by several drugs including morphine, alcohol, and nicotine (Contet, Kieffer & Befort, 2004) and mediates

positive reinforcement following the administration of substances. Therefore it represents an interesting target for the treatment of a variety of substance use disorders (Contet, Kieffer & Befort, 2004). The systematic review on NTX (*Chapter four*) updates and summarizes evidence regarding the effectiveness of NTX and the added value of psychosocial treatment in the NTX maintenance treatment of patients with opioid and alcohol use disorders. The review shows that there is insufficient evidence to refute or confirm the effectiveness of NTX in the maintenance treatment of opioid dependence.

Several studies on NTX have been shown to alter ad lib smoking behavior (Sutherland et al. (1995; Rukstalis et al., 2005; Wewers et al. 1998). It is suggested that NTX may reduce the relative reinforcing effects of nicotine via cigarette smoking in an experimental setting (Rukstalis et al., 2005). The effects in other settings than the laboratory and the effects on the medium or long term are not clear. More NTX trials are needed to assess the efficacy for smoking cessation (David, Lancaster & Stead, 2002).

Studies on alcohol dependent patients showed varied effects of NTX compared to placebo treatment, dependent on treatment duration and outcome parameter. On the medium term, there is strong evidence in favor of NTX with lower relapse rates compared to placebo [overall risk difference 13% [(95% CI): 7 to 18%)]. There is also strong evidence in favor of NTX regarding the percentage of drinking days, but conflicting evidence regarding time to first relapse. There is strong evidence that NTX does not contribute to achieve continuous abstinence and the outcome: time to first drink. On the long term, there is moderate evidence in favor of NTX concerning relapse rate and moderate evidence for the absence of an additional effect on percentage of drinking days and time to first relapse.

A recent review on NTX in the treatment of alcohol dependence demonstrated a short-term increase of nausea, dizziness, and fatigue, when compared to placebo (Srisurapanont & Jarusuraisin, 2005). However, these side effects did not endorse a greater proportion of treatment discontinuation for the NTX group as compared to the placebo group.

In studies among opioid dependent patients, NTX was combined with a broad range of psychosocial interventions, which complicated the evaluation of their

added value. Concomitant psychosocial interventions used in the alcohol studies were mainly cognitive behavioral. There is some evidence that the combination NTX and cognitive behavioral therapy is somewhat better than NTX combined with supportive therapy (Agosti, 1995; Sinclair, 2001), as both NTX and cognitive behavioral oriented programs may operate synergistically to prevent slips from becoming relapses. Meta-regression analysis showed no significant added value of either group or individual psychotherapy. In general, the auxiliary psychosocial therapies failed to prevent dropout and NTX non-compliance.

It is reasonable to expect that the effects of NTX dissipate after discontinuation. In order to achieve sustained success, and consistent with Wiklers' 'extinction' theory (Wikler, 1976), it has been proposed to administrate NTX lifelong (Sinclair, 2001). It has been suggested that pharmacological extinction could only be achieved when NTX is paired with alcohol consumption and therefore should continue indefinitely (Sinclair, 2001). But, according to others (Yoburn et al., 2004), such a continuous opioid receptor blockage can produce receptor up-regulation, which has the potential to attenuate the pharmacological efficacy of NTX (c.f. Overstreet et al., 1999). An alternative strategy would be to employ intermittent or periodical use of NTX (see also Sinclair, 2001), which would imply that patients have to carry a NTX pill with them, but have to take it only when they are likely to drink (i.e. 'targeted use'; Heinälä et al., 2001; Sinclair 1992). Currently, no data are available to choose between these two strategies.

In sum, there is lack of evidence about the effectiveness of NTX alone in the maintenance treatment of opioid and nicotine dependence. There is evidence for the effectiveness and applicability of NTX in the management of alcohol dependence leading to lower relapse rates and a reduction in the number of drinking days on the medium term. However, it should be noted that up to 36% of the NTX eligible participants discontinue treatment within the first 3 months (Srisurapanont & Jarusuraisin, 2005). The treatment attrition hampers the evaluation of NTX on the long term. Therefore, new strategies are needed, which are designed to improve the effectiveness of NTX, such as sustained release preparations (Garbutt et al., 2005).

8.1.3. Discussion of the content of CRA

CRA is a multi-component intervention and most of these components are described in the manuals (e.g. Budney & Higgins, 1998; Meyers & Smith, 1995). CRA asks for an individualized action-oriented style as CRA is grounded in the principles of positive reinforcement; it focuses persistently on opportunities to reinforce the patient, even if these opportunities are small. The therapist needs to be flexible, directive, energetic and engaging in his treatment approach, and should have basic counseling skills, knowledge of the behavioral CRA techniques, supportiveness and empathy. It is the combination of compassion and skills that make CRA work (Meyers & Squires, 2001).

Mental health professionals, such as social workers, have been suggested to employ CRA treatment programs, because their perspective is compatible with CRA in terms of individuals' social situations and resources (Peele, 2004).

In the last three decades CRA has been expanded with a wide range of interventions to create a "menu" or "toolbox" of options (Meyers & Smith, 1995) such as an additional voucher approach, additional social-skill training, self-control training and motivational enhancement (*Chapter two*). Unfortunately, the incremental value of the different components within CRA is still unclear. Further dismantling research on this topic should resolve this issue.

In the contemporary literature CRA has been successfully combined with contingency management by vouchers. Vouchers were included, because the efficacy of implementing contingencies via CRA procedures is often compromised by lack of consistency, and temporal delays. This might even happen when significant others are involved to promote daily routine. Therefore, to maintain the power of contingencies, a formal program such as CRA combined with vouchers seems favorable to manage the sampling, frequency and accuracy of administered and implemented contingencies in the patients' own community (Higgins, 2003).

The dissemination of CRA has been limited and this is not due to high costs, as CRA has been associated with medium-low costs (Finney & Monahan, 1996). Instead, it could be due to perceived limited additional value to common practice,

incompatibility with common practice, or perceived unrealistic levels of clinical expertise. For instance, the presence of generally used elements such as coping skills and training interventions may give therapists the idea that they already use CRA (because of the overlap with concurrent evidence based therapies). On the other hand, seasoned health care providers may be reluctant to adopt CRA, because of certain incompatibilities with existing treatments. Both claims might lead to reluctance to substitute their already embraced therapy assumptions and practice (Miller & Meyers, 2001, p.167). Therefore, it should be made clear what the differences and similarities of CRA are compared to other therapies.

In addition, Miller and Meyers (2001, p. 162) state that different therapists including novice graduate students were capable of scrutinizing the CRA methodology and delivering CRA therapy in several trials. The transfer of CRA can be achieved with rather consistent results (Miller and Meyers, 2001, p. 163).

8.2. Limitations

The studies included in this dissertation contain reviews and empirical studies addressing the efficacy of CRA and NTX. The findings yield consistent and similar outcomes to outcomes mentioned in the literature. The comprehensive reviews applied an elaborate electronic search, which identified recent studies on both CRA and NTX. The three empirical studies on CRA and NTX were aimed to foster abstinence on two different substance use disorders (i.e. opioid and nicotine). However there are some limitations.

Firstly, despite the effectiveness of CRA, it has not been widely used. At this time, there are only three research groups that have studied CRA systematically: the groups of Azrin, Miller, and Higgins. More research groups should be involved in examining CRA to prevent bias and to increase generalizability.

Secondly, in the conceptual analysis, in most included protocols, the descriptions of the CRA programs are rather brief. In general, the protocols yielded insufficient information about the amount and the proportion of time that was spent on the various CRA components. Furthermore, only limited attention is

paid to treatment integrity. Too few data are available with regard to treatment intensity and total treatment consumption, and subsequently there are no data on a possible dose-response relationship with the targeted outcome.

Thirdly, there were only a limited number of subjects in two of the three empirical studies. The pilot study on the effectiveness of NTX in opioid dependent patients and the NTX study on smoking cessation were underpowered. In addition, both studies on the effectiveness of CRA combined with NTX in opioid-addicted patients did not use a randomized design with adequate concealment. Above all, in the pilot study on the effectiveness of NTX in opioid dependence, a selection occurred by charging money in order to take part in the treatment with NTX. Selection bias was also present in all three empirical studies by the inclusion criterion of bringing in a significant other. This selection bias may affect the generalizability.

In the review on NTX it should be noted that the US Food and Drug Administration (FDA) approved NTX on the basis of its pharmacological profile, without any positive double blind study, because it cannot be effectively blinded in heroin dependent patients. Patients can simply take a test dose and discover what condition (i.e. NTX or placebo) they are allocated to. Several publications show a clear effect of NTX when patients are compliant to the medication regime (Kirchmayer et al., 2004). These studies demonstrate that NTX compliance is dependent on the population (business executives, physicians and health care professionals; Washton et al, 1984), the context of NTX prescription (probation or parole; Cornish et al, 1997), and the cultural and therapy setting (family therapy; Fals-Stewart & O'Farrell, 2003; Resnick, Washton & Stone-Washton, 1981; family involvement; Krupitsky et al., 2004). To increase the efficacy of NTX, further research in the identification of subgroups or controlled conditions of drug delivery systems seems warranted.

Fourthly, the smoking study was characterized by side effects of the high dose of NTX and a relative high drop-out leading to a collapse of the conditions in CRA versus no-therapy. Although not statistically significant, CRA combined with NTX produced higher cessation rates than NTX alone. This corresponds with outcomes of other studies on CRA (Miller et al., 2001 p. 162).

Another limitation concerns the volume of conducted studies included in the subgroup analyses of the CRA review. The clinical heterogeneity of the studies and the relative scanty number of RCTs hindered the subgroup analyses in a variety of substance use disorders. In addition, the inclusion of several pharmacological agents and the contingency management program also produced heterogeneity. Some of the studies only contained small sample sizes and must be considered as pilot studies.

8.3. Clinical and research considerations

8.3.1. Treatment goals in the treatment of substance use disorders

In general, the primary goal for the treatment of many patients with substance use disorders is focused on sustained abstinence. Whilst abstinence is considered as the main goal in the alcohol treatment, empirical studies have demonstrated that harm reduction approaches, for instance, to alcohol problems are at least as effective (Marlatt & Witkiewitz, 2002). Nevertheless, little attention has been paid to the advantages of integrating both abstinence and non-abstinence goals as part of a comprehensive continuum of treatment for patients with alcohol problems (Ambrogne, 2002) or other problems related to substance use disorders.

Viewing alcohol problems on a continuum, ranging from abstinence to harm-reduction, might lead to a reduction of alcohol-related nuisance at the population level (World Health Organization, 2001). Providing a continuum of options from abstinence to moderation is consistent with stepped-care approaches that offer treatment with increasing levels of intensity, restrictions, and cost (Marlatt, 1996; Sobell & Sobell, 1993). Furthermore, it provides a useful framework to motivate patients in their process of change to reach achievable goals (DiClemente, 1999), and might be helpful for individuals encountering decisions regarding their alcohol use (Rosenberg & Davis, 1994). The harm reduction approach provides low threshold and flexible treatment options with a variety of goals and

approaches, tailored to the needs of the individual patient (Marlatt & Witkiewitz, 2002).

An important pharmacological option to foster abstinence is acamprosate. It has been demonstrated that acamprosate with counseling resulted in more abstinent days, reduced drinking days, and lower drop-out rates when compared to placebo (e.g. Sass, Soyka, Mann & Zieglgansberger, 1996; Schuckit, 1996; Verheul et al., 2005). It should be noted that adding intensive individual psychosocial treatments produced no improvement when compared to acamprosate and infrequent consultation with a physician (Hammarberg et al., 2004). Acamprosate is believed to maintain abstinence by blocking the negative craving that alcohol dependent patients experience in the absence of alcohol (Mann, 2004). From a clinical perspective, acamprosate appears to be especially useful in a therapeutic approach targeted at achieving abstinence, whereas NTX seems more indicated in treatment focused on controlled consumption (Bouza et al., 2004). In addition, NTX is thought to decrease relapse to heavy drinking by attenuating the rewarding effects of alcohol (Srisurapanont & Jarusuraisin, 2005).

NTX has also been compared to acamprosate. NTX produced better effects than acamprosate in a sample of moderate alcohol dependent patients in terms of relapse rates, cumulative abstinence, number of drinks consumed at one time, percentage of heavy drinking days and severity of craving (Rubio et al., 2001). The benefit of NTX over acamprosate has been confirmed in a study with four treatment arms in terms of time to first drink and time to relapse (Kiefer et al., 2003). The combination of NTX and acamprosate was significantly more effective than acamprosate alone (Kiefer et al., 2003).

In another comparison, it has been shown that disulfiram was more associated with abstinence than was NTX, with twice as many abstinent patients (De Sousa & De Sousa, 2004). Conversely, the patients in the NTX condition had significantly lower craving scores. Disulfiram has traditionally been used as part of abstinence-oriented treatment programs in the treatment of alcoholism, but with limited effectiveness due to poor compliance (Fuller & Gordis, 2004).

However, in alcohol dependent patients with a co-morbid psychiatric disorder, the combination of NTX with disulfiram was not more effective than each

medication separately and both separate medication were equally effective (Petrakis et al., 2005).

Opioid addiction is a chronic, relapsing disorder with treatment goals including crisis intervention, cure, or recovery (detoxification, relapse prevention) and care or partial remission (stabilization and harm reduction) (Van den Brink & Van Ree, 2003), whereas abstinence is often not a feasible goal for all opioid dependent persons (American Society of Addiction Medicine, 2001). In contrast to other substance use disorders, the management of opioid dependency is currently dominated by the harm reduction approach (Van den Brink, Goppel & Van Ree, 2003).

Harm-reduction-based treatment with opioid-agonist such as methadone is considered as the first choice of treatment. At appropriate doses, methadone maintenance is effective in retaining patients in treatment and suppressing heroin use (Amato et al., 2005; Sullivan, Metzger, Fudala & Fiellin, 2005). Furthermore, methadone treatment is associated with fewer injections and injection-related HIV risk behaviors and lower rates of HIV prevalence and incidence (Sullivan, Metzger, Fudala & Fiellin, 2005). Most patients require at least 80-120 mg/d of methadone to achieve these effects (Joseph, Stancliff & Langrod, 2000). Patients may require opioid substitution for many years up to lifelong (Fiellin & O'Connor, 2002; Goldstein, 1991; Joseph, Stancliff & Langrod, 2000). Consequently, for the majority of opioid dependent patients methadone maintenance is considered an effective long-term modality (American Society of Addiction Medicine, 2001). Two other medications have been used for stabilizing heroin users: buprenorphine and levomethadyl acetate (LAAM). The advantage of the pharmacological properties of LAAM and buprenorphine over methadone is the possibility of less-than-daily doses (Johnson et al., 2000). Due to clinically significant changes in heart conduction (prolongation of the QTc interval leading to Torsades de Pointes, a distinctive form of polymorphic ventricular tachycardia; Deamer et al., 2001), concerns have been raised, eventually resulting in a termination of the distribution of LAAM in the Europe in 2001 (Van den Brink & Van Ree, 2003) and the USA in 2004 (Newcombe et al., 2004). It has been suggested that this issue about QT

prolongation with LAAM should be resolved (Ritter et al., 2003). It must be noted that at the same time, methadone also has been associated with cardiac repolarisation (Kaufman et al., 2002; Krantz et al., 2002; Ritter et al., 2003).

The other option for substitution treatment is buprenorphine. Because these tablets can be dissolved and injected, they can have an abuse potential (Varescon et al., 2002). Consequently, a novel tablet has been developed that contains a 4: 1 buprenorphine-naloxone ratio, to diminish the abuse potential (Stoller et al., 2001). Such a tablet dispensed by sublingual route produces a regular expected (partial agonist) effect. In contrast, when this tablet is dissolved and injected intravenously it produces an opioid (antagonist) withdrawal syndrome.

A recent comparison between buprenorphine and methadone yielded better outcomes for patients who received methadone in terms of treatment retention and periods of sustained abstinence from illicit opioids and cocaine (Schottenfeld et al., 2005). Thus methadone maintenance is still considered to be the most effective treatment in terms of treatment retention and the cessation of illegal opioid use (Amato, 2005; Gossop et al., 2001).

A unique combination is methadone maintenance and the co-prescription of heroin. Research has demonstrated that this combination is feasible and more effective in reducing physical, mental, and social problems of treatment resistant methadone patients than continuation of methadone alone (Van den Brink et al., 2003). Furthermore, in this specific population, this combination is cost effective compared to methadone alone (Dijkgraaf et al., 2005). But these favorable outcomes might be partly produced due to accessible methadone maintenance programs (Ferri, Davoli & Perucci, 2005).

It has been argued that stigma and bias directed at the programs and the patients have hindered expansion of substitution treatment, which makes the treatment system vulnerable to shifting community support and abrupt, politically-driven changes in policy (Bell et al., 2002).

Opioid substitution treatments are currently provided in special drug treatment settings. In order to make this treatment more available, accessible and attractive, the primary care setting seems a valuable option. It has been demonstrated that

the physician's office may be the alternative site for these treatments (Fiellin et al., 2001). In addition, the results support the feasibility and efficacy of transferring stable opioid-dependent patients receiving methadone (Fiellin et al., 2001) and buprenorphine (Fiellin et al., 2002) maintenance to primary care physicians' offices for continuing treatment (Fiellin et al., 2001).

Abstinence oriented treatments should be attempted only when the patient is motivated, and with the availability of adequate supervision and support (American Society of Addiction Medicine, 2001). Detoxification should be followed by psychosocial treatment, otherwise it may lead to rapid relapse and it may not be as effective as maintenance (Fiellin et al., 2004).

Commercial organizations, such as CITA or the Waismann Institute, are mainly abstinence focused and are only accessible for a subgroup of patients who are capable of financing treatment themselves. Treatments, such as rapid opioid detoxification, cost up to $ 8500. It has been reported that 12-18 months after initial treatment, 60-65% of patients are still opiate-free (McKey, 1997, p. 20-22; Wielenga, 1999). These favorable outcomes were substantiated by a report from a study conducted in a private clinic, which was not covered by health insurance. In this study on the one-year relapse rate of persons detoxified using this ultra rapid method in conjunction with NTX maintenance and counseling, 57% of patients had not relapsed (Rabinowitz, Cohen & Kotler, 1998).

Comparable results were obtained in the pilot study employing rapid opioid detoxification and CRA (*Chapter five*). Although inconclusive, an essential factor in this study may have been charging money in order to participate. The robust treatment effects might be due to selection (bias) of already motivated subjects who are willing to enter the rehabilitation process. As suggested, a NTX treatment might be especially effective in highly motivated participants who fear severe consequences in case they do not stop taking opioids, for instance health-care professionals, who might lose their job or parolees who risk re-incarceration (Kirchmayer et al., 2004). Furthermore, these subgroups may be characterized by the presence of a social network including non-substance using significant others (willing to invest and co-participate in treatment), a relatively moderate addiction severity, higher levels of self-efficacy, and the ability to rejoin the community.

8.3.2. Improving treatment outcome

The opioid studies, which employed NTX treatment, asserted that a lack of motivation, compliance and a high dropout rate have corrupted the outcomes in non-specific samples (Kirchmayer et al., 2004). Recent findings in Australia showed that only 4% of the patients in NTX maintenance remained in treatment after 6 months (National Drug and Alcohol Research Centre, 2001). Poor treatment compliance with pharmacotherapy is a widespread problem for patients with substance use disorders. It undermines treatment benefits and produces impaired outcomes (c.f. Haynes 2001; O'Brien & McLellan, 1996; Weiss, 2004). Moreover, the lack of compliance is considered as a major factor limiting the clinical value of pharmacological agents, such as NTX in the management of opioid dependence (Rothenberg et al. 2002) and disulfiram in alcohol treatment (Fuller et al. 1986; Fuller & Gordis, 2004). Compliance is especially important in chronic diseases (DiMatteo et al. 2002) such as substance use disorders (Leshner, 1997; McLellan 2002; Van den Brink & Van Ree, 2003), as chronic disorders need continuous treatment (McLellan, 2002; O'Brien & McLellan, 1996). In general, the effectiveness of pharmacological agents corresponds with the degree of treatment adherence (Vergouwen, Bakker & Koerselman, 2003). Several alcohol studies demonstrated a relation between NTX compliance (and adequate NTX plasma levels) and positive outcomes (Chick et al., 2000; Kranzler et al., 2000; Krystal et al., 2001; O'Malley et al., 1992; Volpicelli et al., 1997).

To improve current treatment outcome there are several potential strategies:

1. The promise of innovative drug delivery systems (Garbutt et al., 2005);
2. The development and application of vaccines (Kantak, 2003)
3. Patient-treatment matching based on clinical variables or via pharmagenomics (Oslin et al., 2003);
4. Combination of pharmacological agents (Kiefer et al., 2003; Besson et al., 1998; Petrakis et al., 2005);
5. Combination of pharmacotherapy and psychosocial treatment (Carroll, 2001).

1. Drug delivery systems

The complexity of dosages and route of administration are important factors that trouble treatment effectiveness. In addition, there is evidence that a reduction in frequency of administration enhances treatment adherence (Vergouwen, Bakker & Koerselman, 2003). A route to govern adequate plasma concentrations of NTX seems to be the insertion of (subcutaneous) NTX implants (Carreno et al., 2003; Foster et al., 2003), to treat both alcohol and opioid use disorders.

To mitigate the widely fluctuating NTX plasma levels (often represented by a saw tooth pattern of plasma drug concentration), a recent development encompasses the use of extended-release formulation of NTX (i.e. naltrexone depot, DrugAbuse Sciences (DAS); Vivitrex®, Alkermes). This compound was developed by encapsulating NTX into single subcutaneous injectable, biocompatible, biodegradable (see Anderson & Shive, 1997) polymer microspheres (polylactide-co-glycolide-based) (Bartus et al., 2003). Basically, the polylactide-co-glycolide microspheres establish a depot at the injection site from where NTX is slowly released and rejuvenated. Pharmacokinetic analysis confirmed that therapeutic levels of NTX could be maintained when injections are administered only monthly (Johnson et al., 2004). This long-acting agent seems safe and tolerable in the treatment of alcohol dependent patients within 6 months follow up (Garbutt et al., 2005; Johnson et al., 2004), but also over an 18-month period (Gastfriend, 2005). In addition, the injection of NTX reduced heavy drinking among patients during 3 (Kranzler et al., 2004) to 6 months (Garbutt et al., 2005) of therapy when compared to placebo. Unfortunately, the effect of a sustained release formulation of NTX (depot injection) was not directly compared to the effects of the original treatment with NTX tables (Van den Brink, in press).

To improve patient convenience and while still controlling drug release, new innovative drug delivery vehicles are currently under development. Oral delivery is the preferred route of drug administration (Tao, Lubeley & Desai, 2003) and the efficacy of polylactide-co-glycolide based oral drug delivery systems have already successfully been applied (Ain, Sharma, Garg & Khuller, 2002). Recent advances encompass non-invasive transmission options, such as oral, pulmonary, and transdermal/transmucosal systems, which seem more favorable than injectable

release formulations or more invasive forms such as implants to reduce dosing regimens.

On the other hand, there is an emergence of controlled biodegradable polymeric implantable microchips (once implanted no removal), which is capable of achieving complex drug-release patterns in response to specific stimuli such as PH, temperature and enzymes. These devices are currently being developed by the use of micro- and nanotechnology (Tao & Desai, 2003).

These release mechanisms provides on-demand-controlled release of single or multiple drugs (Santini, Cima & Langer, 1999). Additionally, pharmacological agents are stored in micro reservoirs covered by a thin anode membrane and released when the anode membrane is dissolved by means of electrochemical dissolution. The development of such a biodegradable controlled-release microchip would be advantageous for long-term treatment of conditions when sustained drug release is mandatory (Richards Grayson et al., 2003; Tao & Desai, 2003).

Similar to the use of other drug delivery systems, it must be stressed that the efficacy is coupled with the motivation of the individual. In addition, it is likely to work best as part of a comprehensive treatment program (Garbutt et al., 2005).

2. The development and application of vaccines

A novel treatment option is the application of vaccines, which is aimed to eliminate problematic substance use by altering the pharmacokinetics of the substance to prevent substances from entering the brain (Gorelick, 2004). As there are currently no effective pharmacological treatments for cocaine dependence, immunization treatments may be an interesting option (Gorelick, 2004; Kantak, 2003). Most work has been conducted with vaccines and antibodies targeted against cocaine (e.g. Vaccine TA-CD) and nicotine (e.g. TA-NIC) (Kantak, 2003). Vaccines operate by inducing drug-specific antibodies in the bloodstream that bind to cocaine or nicotine in the blood, resulting in large molecules that are incapable of entering the blood barrier. As a result, the psychotropic substance is prevented to exert reinforcing actions in the brain. The nicotine or cocaine molecules are too small to be antigenic. Consequently, these

molecules have to be paired to build a large carrier protein, to mimic the psychotropic properties and to serve as an antigen. Two human studies have applied succinylnorcocaine covalently bonded to recombinant cholera toxin B subunit to create cocaine antigenic (Vaccine TA-CD) (Kosten et al., 2002). These vaccines were administered by intramuscular injections of up to three 100-mcg doses and five 400 mcg TA-CD vaccine doses, to provoke antibody responses. It was shown that the maximum antibody response occurred between 70 and 90 days after vaccination, with cocaine antibodies persisting for at least six months (Martell, 2004). It was concluded that the immunization was well tolerated and the peak antibody level was negatively associated with the degree of cocaine use. In 2003, a clinical trial was started to treat methadone-dependent cocaine using persons. In this clinical study up to 132 patients are being recruited to compare the efficacy of the vaccine TA-CD to placebo (Xenova group plc, 2005). Other, more or less similar, technological innovations are currently developed to treat substance use disorders including cocaine, methamphetamine, and nicotine dependence (Haney & Kosten, 2004).

It is expected that this expansion of pharmacological treatment arrangements, should be applied in concert with psychosocial programs, just the same as other chronic diseases, and should be available only for highly motivated patients (Kantak, 2003).

3. Patient-treatment matching

The search for predictive variables seems an important avenue to select or match specific patients to different treatment modalities in order to enhance treatment outcome and reduce costs. Large numbers of studies have been conducted into the isolation of possible predictors of success in substance abuse treatment (e.g. Alterman et al., 2000; Brewer et al., 1998; Ooteman et al., 2005; Siqueland et al., 1998). In general, reviews reveal that there are very few pre-treatment- or in-treatment variables that account for a substantial part of the variance in the primary outcome variables. Certain variables that are unidentified or unrelated to theoretical grounds may be strongly related to successful outcome. In this

respect, there is a need for identifying phenotypic indicators of the underlying myriad of genetic, psychological and social factors. In order to align specific pharmacotherapy to subgroups of alcohol dependent patients, it has been shown that specific subgroups, based on variables such as baseline psychopathology and a typological differentiation, produced improved outcome with either NTX or acamprosate (Kiefer et al., 2005). Moreover, it has been demonstrated that the outcomes of a subgroup of patients with a biological vulnerability, which is coupled with overall poor treatment effects, can be improved with NTX treatment. Additionally, the type of alcoholism should be assessed before choosing the pharmacological strategy (Rubio et al., 2005).

A new, more specific, way to increase the effectiveness is to determine the association between certain genetic polymorphisms and treatment outcomes in alcohol-dependent patients (Oslin et al., 2003). Programming the μ-opioid receptor might play a pharmacogenetic role in the differential response to an opioid antagonist (Oslin et al., 2003, Oswald et al., 2004). More generally, it has recently been suggested that genotypes and endophenotypes are more likely to be useful matching variables than phenotypicalor clinical characteristics (Ooteman et al., 2005). Based on pharmacogenomics, several (new) pharmacological agents are currently subject of research, particularly for specific types of alcoholism (Kenna, McGeary & Swift, 2004).

4. Combination of pharmacological agents

Another option to improve outcomes is the combination of available agents, as the combination of acamprosate with NTX or disulfiram may lead to improved outcomes (Fuller & Gordis, 2004; Besson et al., 1998; Kiefer et al., 2003). NTX and acamprosate, especially in combination, yielded better outcomes in term of relapse rates than placebo or solely administered acamprosate (Kiefer et al., 2003). NTX administration is associated with increased plasma acamprosate levels (Johnson et al., 2003). It must be noted, however, that this combination of medications might produce more side effects (Bouza et al., 2004). The combination generated no statistically significant advantage when compared to

only NTX, although the combination showed a tendency for a better outcome. For that reason, the combination of NTX and acamprosate may be considered as somewhat favorable (Kiefer & Wiedemann, 2004; Scott et al., 2005).

5. Combination of phamacotherapy and psychosocial treatment

The term *compliance* is associated with a passive patient role (Kristeller and Rodin, 1984). In contrast, the term *adherence* implies an active patient participation with autonomy and mutuality in performing treatment actions (Lutfey & Wishner 1999; Meichenbaum & Turk, 1987) and is often preferred in the literature. Behavioral choices affect adherent behavior and consequently determine the course and severity of reoccurrence. These choices can be considered as a result of communication between a clinician and a patient, and are sometimes defined as shared decision-making (Rasmussen Wilkinson & Williams, 2002). In this respect, both clinician and patient share responsibilities for adherence (Patel & David, 2004).

Unfortunately, it has been asserted that only a few physicians acknowledge that they might contribute to their patients' non-adherence (Cochran & Getlin, 1988; Stone, 1979). Besides, several studies have indicated a firm discrepancy between physicians' and patients' understanding and appraisal of physician-patient interaction (Dimatteo, Reiter & Gambone, 1994; Frank, Kupfer & Seigel, 1995; House, Pendelton & Parker, 1986; Merkel, Rudisill, & Nierenberg, 1983). This is in stark contrast with the need for a positive patient clinician relationship, which is considered to be central to the success of any strategy for improving adherence (Heinssen, 2002; Weiss, 2004). It seems plausible that many physicians have only limited familiarity with effective strategies and recommendations. In this respect it should be stressed that single specific strategies such as psycho educational interventions, which focus primarily on imparting knowledge, have proved to be largely ineffective (O'Brien & McLellan, 1996; Patel & David, 2004; Weiss, 2004).

Because adherence is influenced by multiple factors, a combination of strategies is most likely to produce favorable results (Weiss, 2004; Williams et al.

1998). Individual interventions should specifically target the patient's beliefs and attitudes concerning the illness and medication by using cognitive motivational therapy and behavioral modification approaches (Patel & David, 2004). Behavioral therapies, such as voucher management, can be targeted to address non-adherence of pharmacotherapies, such as NTX in problematic alcohol using patients (Higgins & Petry, 1999; Petry et al., 2000) and detoxified opioid dependent individuals (Carroll et al., 2001, 2002; Preston et al., 1999). Consequently, targeted behavioral therapies may play a substantial role in broadening the utility of available pharmacotherapies (Carroll et al., 2002). However, these behavioral regulation techniques may be effective only on the short/medium term, as the power of contingency management dissipates after discontinuation. Long-term prescriptions are strongly associated with autonomous motivation, as autonomous regulation has been found to account for 68% of the variance in adherence (Wiliams et al., 1998). A cognitive motivational treatment should support patients' autonomy by addressing initiative, acknowledgment of the patients' feelings, minimizing the pressure to behave in a restricted way, offering choices about treatment regimens, and to provide meaningful rationales for suggested behaviors (Deci et al., 1994).

A dilemma to address adherence by physicians is that they do not have the function to serve as mental health professionals. Moreover, the interventions needed to augment adherence encompass the interplay of psychosocial interventions and are part of the professional domain of mental health professionals (i.e. psychologists, psychiatrists). Accordingly, due to time constraints and lack of skills to employ psychosocial interventions, the role of the physicians' clinical involvement should be concentrated on the prescription of the medication, according to professional standards. An alternative is the employment of specially trained nurses or care managers, who monitor the patient, implement recommended medical management, foster structured coping skills, and closely collaborate with the physician and other health and social services (c.f. Roy-Byrne et al., 2005; Williams et al., 2004).

In CRA treatment, this issue is outlined in detail (see Meyers & Smith, 1995, pp. 57-77; Sisson & Azrin, 1986, pp. 245-247). The involvement of the subjects'

physician is only to pre-examine eligible patients and when medically cleared, the patient can be prescribed the specific medication (e.g. disulfiram). In communication between the CRA therapist and physician it should be noted that the medication is only a part of the entire treatment and results from a consensual agreed-upon plan between the CRA therapist and the patient. In CRA treatment it is suggested that a physician monitors the patient only medically and that the CRA therapist incorporates adherence within the whole set of CRA interventions. In the Netherlands, this procedure to guide the CRA integrity should be reflected in the allocation of tasks and warrants dialogs between physicians, health professionals, and policymakers to deal with issues such as responsibilities, monitoring, and reporting on possible adverse events/side effects.

8.3.3. Principles of behavioral reinforcement

It has been suggested that repeated exposure to substances results in deregulation of brain reward pathways (Koob & Le Moal, 1997; Koob et al., 2004). There are qualitative and quantitative differences in increases in dopamine in the brain induced by substances and other (natural) reinforcers. Addictive substances are more robust in terms of magnitude (five- to tenfold) and duration, when compared to naturally induced reinforcers (Wise, 1998, 2002). Due to neural adaptations, the individual is more responsive to dopamine as a result of addiction and less sensitive to the physiological increase in dopamine produced by natural reinforcers (Volkow et al., 2004; Volkow & Li, 2004). As a result there is a reduction in the sensitivity of reward circuits in drug dependent individuals to natural reinforcers (Mohn, Yao & Caron, 2004; Volkow, Fowler & Wang, 2003), but also to monetary rewards (Martin-Solch et al., 2001).

Substance abuse disorders lead to disruption of several brain regions, which may undermine volitional control (Volkow & Li, 2004), or impair the process of decision-making (Fellows, 2004). It has been shown that the value of delayed reinforcers is considered to be worth less than the value of immediate reinforcers in individuals with substance use disorders, when compared to non-substance using persons (Bickel & Marsh, 2001). More recent data have confirmed this

finding, and have shown that discount rates vary with the preferred substance of use (Kirby & Petry, 2004). Therefore it seems evident to consider drug dependence as a reinforcement disorder (Higgins, Alessi, & Dantona, 2002). This raises the issue whether it is possible to outweigh substance related rewards by contrived reinforcers or reinforcement derived from the natural environment.

First, heritable or genetic factors account for, in general, half of the total variability in substance abuse (Uhl & Grow, 2004). In addition, the remaining variability is influenced by environmental factors (Lessov et al., 2004). The posited genetic risk appears to be represented by a large number of genes, but with each of them manifesting small or modest effects (Comings & Blum, 2000; Enoch, 2003; Lessov et al., 2004). There is a firm indication that the physical development is a process of interaction with the environment and less solely determined by genes (Margaron, 2004). However, a subgroup of individuals with genetic susceptibility may develop addiction rapidly after initial substance use (Hiroi & Agatsuma, 2005). But this genetic risk may be differentially expressed depending on the environmental conditions (Lessov et al., 2004).

Second, owing to micro-array technology, about 100 genes have been identified with altered expression after administration of substances (Kuhar, Joyce & Dominguez, 2001). Nevertheless, based on the relatively limited prevalence of addiction, neural adaptations induced by substance abuse do not fully explain the variability in substance dependence. In other words, prolonged exposure is not a sufficient condition for addiction (Hiroi & Agatsuma, 2005). Evidence is provided by the classic epidemiological studies of Robins, who revealed that only a minority of American soldiers who initiated heroin use in Vietnam remained addicted after returning to the US. In general, usage decreased to pre-Vietnam levels (Robins, Helzer & Davis, 1975; Robins, 1993).

Hence, the environment plays a fundamental factor in the progression of infrequent substance use to substance dependence. Modifying the environment of the addicted individual seems essential in treating substance use disorders. Although there is an insensitivity in brain regions in patients with substance use disorders that are involved in processing reward information, such as monetary rewards (Martin-Solch et al., 2001), principles of behavioral reinforcement such as

CRA, and the incentive approach with contrived reinforcers, hold consistently strong evidence to be effective. Two derivations of behavioral reinforcement are discussed:

Voucher management

Despite three decades of research, in which a substantial amount of compelling evidence is accumulated, the incentive approach is still not implemented in routine clinical practice. Much of the research has focused on vouchers as a reward system. In general, the voucher procedure is characterized by an escalating pay schedule to promote stable abstinence. When substance use occurs, the pay schedule is reset. In this way rewards are provided to initiate and to endorse long-term abstinence.

There is, however, a serious debate on implementing contrived or tangible reinforcers. The voucher is often considered as (too) expensive to employ and manage (Petry & Smcic, 2002). These costs are considered as an important factor, which has hindered its dissemination (Petry et al., 2000). An avenue to reduce costs encompasses intermittent reinforcement in which only a certain proportion of the target behavior is paired with tangible reinforcers. Several studies that applied this system introduced prizes such as CD players, watches, etc, to illustrate the power of the incentive approach at low cost (Petry et al., 2000). Intermittent reinforcement has proven to be effective for treating cocaine users at low costs (Petry et al., 2004).

The effectiveness of the voucher approach is attenuated when the magnitude of reinforcement becomes too low (Silverman et al., 1999). Also, the definition of a high threshold target outcome (i.e. abstinence), especially for some subpopulations (i.e. heroin dependent poly-drug using persons), may result in poor sampling of rewards and, as a consequence, reduce the effectiveness (Downey et al., 2000; Piotrowski et al., 1999; Schottenfeld et al., 2005; Silverman et al., 1996). Possible resolutions encompass defining lower threshold behavior for earning a reward, such as reductions in use instead of abstinence, or providing high magnitude monetary vouchers (Preston et al., 2001; Dallery et al., 2001).

Costs are probably not the only reason for the lack of dissemination in regular clinical practice. There may be other reasons addressing the moral or social domain. Paying persons with substance use disorders for not using drugs may be considered similar to paying thieves for not to stealing (Van den Brink, 2003).

Vouchers can be used to acquire reinforcers on a broad variety of items and services, and are just like money a conditioned reinforcer. The actual paper bills are in themselves not reinforcing, but due to the pairing with preferred goods and services they become reinforcers. In this respect, money, instead of vouchers, seems a more direct option when it is paired with certain target behaviors. An advantage of vouchers over money is that voucher management is associated with items and services that are specifically non-substance related. With money as the reinforcer this pairing seems uncontrollable.

This relation between earned items and natural reinforces is considered valuable in CRA combined with voucher management. The effectiveness on the long term is probably related to the implementation of sufficient non-substance related sources of reinforcement that occur naturally in the environment.

CRA

Reinforcement can also directly be emitted by the sampling of alternative rewarding behaviors (e.g. engaging in reinforcing recreational and social activities), which can be captured in the natural community to outweigh substance-using behavior (Correia, Benson & Carey, 2005; Van Etten & Higgins, 1998). These reinforcers should consistently be administered contingent on clearly defined target behavior or stimuli (e.g. outcome of urinalysis, pre-defined social interactions, etc) in a predictable way. It must be noted that alternative non-substance related behaviors should have a high intrinsic magnitude of reinforcement. Additionally, these alternative behaviors should have a high density and thus should be closely grouped together in time (Hunt & Azrin, 1973). There is a wealth of unexplored opportunities to assess what the patient values in terms of items, services, and privileges. The currency can be sampled by means of checklists such as the ‘Leisure Interests Checklist’ (Rosenthal & Rosenthal, 1985) or ‘Pleasant Events Schedule’ (MacPhillamy & Lewinsohn, 1982) and the

specifically designed questionnaire for the Dutch addiction treatment services the 'Plezierige Activiteiten Lijst' (Koks & Roozen, 2005) to increase engagement in substance-free behaviors.

8.3.4. The role of rewards on intrinsic motivation

In the past three decades of research on CRA, it has been shown that the cognitive behavioral concept has been expanded with elements such as motivation enhancing interventions. The creation of cognitive dissonance can clearly be distinct within motivational interventions (Draycott & Dabbs, 1998). More than four decades of research has shown that cognitive dissonance is an important motivator of human action (Aronson, Wilson & Akert, 2002, p. 174). According to cognitive dissonance theory (Festinger, 1957), individuals pursue for consonance among their cognitions, to avoid discomfort or arousal. As there is strong support that dissonance causes physiological arousal (Devine, 1998; Zanna & Cooper, 1974). The crucial element is the relationship between cognitive elements and what subsequently happens when these elements are inconsistent with one another (Kiesler, Collins & Miller, 1969). An inconsistency between attitudes or behaviors produces discomfort and enhances the motivation to eliminate the dissonance. This is especially the case in situations where a certain behavior threatens self-images (Aronson, 1998). In the case of a discrepancy between attitudes and behavior, it is most likely that the attitude will change to accommodate the behavior.

Two factors affect the strength of the dissonance: the number of dissonant beliefs, and the importance attached to each belief. There are three ways to decrease dissonance: (1) reduce the importance of the dissonant beliefs, (2) add more consonant beliefs that outweigh the dissonant beliefs, or (3) change the dissonant beliefs so they are no longer inconsistent.

Dissonance theorists point to a number of phenomena that demonstrate attitude changes that preserve some harmony between past acts and present attitudes. Some involve a cognitive reevaluation that occurs after some irrevocable decision has been made. If a person has to choose between two

incompatible beliefs or actions, and both options are equally attractive, the final decision will lead to dissonance. The option that is finally chosen will seem more attractive and the one that was rejected will seem less attractive than it did before (Brehm, 1956; Knox & Inkster, 1968).

People often make considerable sacrifices to attain a goal. According the dissonance theory, the goal will be esteemed more highly the harder it was to reach (Aronson & Mills, 1959). Derived from the dissonance theory, there is evidence for the original suffering-leading-to-liking hypothesis (Cooper, 1980; Gerard & Mathewson, 1966). People who have made a great sacrifice to attain some goal will value it more than those who achieved the goal with little effort. Furthermore, attitude change is more likely in the direction of less incentive (less external justification), which in turn produces lower dissonance (Cohen, 1962; Festinger & Carlsmith, 1959; Leippe & Eisenstadt, 1994, 1998). In other words, the smaller the reward or incentive, the greater the change of attitude. It is noteworthy that the dissonance theory is incongruous to behavioral theories that predict greater attitude change consistent with increased incentive (i.e. reinforcement approach).

Laboratory and clinical research have shown that abstinence reinforcement procedures are effective in governing substance-abusing behavior (Higgins, Heil & Plebiani Lussier, 2004). According to these studies, reinforcement is crucial to the success of behavioral modification. Within this framework, it has been demonstrated that contrived reinforcers, such as vouchers, are effective in the treatment of alcoholism (e.g. Petry et al., 2000), cocaine dependence (e.g. Higgins et al., 2003), opiates (e.g. Silverman et al., 1996) and marijuana (e.g. Budney et al., 2000). Although the effects of the reinforcement principles were clear for many decades, clinical research on substance use disorders waned after the seventies, but resurrected in the nineties (Higgins, Heil & Plebiani Lussier, 2004 p. 433).

In the seventies a "cognitive revolution" occurred in the behavior therapy (Mahoney, 1974), which exerted a substantial influence on the behavior therapy and behavioral science. In this tradition, the importance of motivation has been

promulgated. The widely used Transtheoretical Model of Change (Prochaska & Diclemente, 1986), characterizes vital variables as psychological mediating mechanisms that operate primarily within the subject (Vuchinich & Tucker, 1998 p. 102). Hence, it seems that motivational interventions focus on self-reevaluation and consciousness raising while more behavioral approaches place accent on stimulus control and contingency management (Davidson, 1998 p. 33).

There is a fundamental philosophical and theoretical difference between cognitive and contingency oriented treatment modalities (De Mey, 2003), but these treatment modalities seem to interact. Behavioral research showed that treatment effects remain discernible for months following discontinuation of an incentive program. So it seems that there must be changes in "motivation" underlying this effect (Higgins, 2003). Nevertheless, this finding seems to conflict with results of nearly three decades of research. It has been demonstrated that when various types of external rewards, such as money, are administered to perform an activity, it discounts intrinsic motivation (Deci, 1971; Deci et al., 1999). Similar findings have been observed in detoxified opioid-dependent participants who were assigned to contingency management to improve NTX adherence. These participants reported significant reductions in readiness to change compared with participants assigned to control NTX treatment (Carroll et al., 2002).

A review of 128 studies examined the effects of extrinsic rewards on intrinsic motivation (Deci et al., 1999). A convergence of findings with previous meta-analyses (Rummel & Feinberg, 1988; Tang and Hall, 1995; Wiersma, 1992) asserted that tangible extrinsic rewards and all expected rewards are detrimental to intrinsic motivation under most circumstances (for discussion see Eisenberger, Pierce & Cameron, 1999). Intrinsic motivation is defined as a psychological need for autonomy and competence. It has been proposed that when rewards are interpreted as controllers of behavior, or as indicators of competence, this will lead to a decrease in intrinsic motivation. When rewards are viewed as positive information (the feedback should be process oriented and address the value of the performance) and when they typically occur unexpected, they provide an

affirmation of competence (Deci et al., 1999; Ryan & Deci, 2000). But it is not always clear how intrinsic motivation affects performance.

Recent research on opioid dependent patients showed better outcomes for contingency management during treatment than for cognitive behavioral therapy (week 17). But at distant follow-up points (weeks 26 and 52), the superiority of contingency management procedure over the cognitive behavioral procedure disappeared (Rawson et al., 2002). More recently, this finding has been replicated (Rawson et al., in press). It might be concluded that the external reward system is effective on the medium term and, with delayed effect, is crucial to address the patients' autonomy to foster long term changes by means of a cognitive motivational treatment (c.f. Williams et al., 1998). Therefore both treatments may be sequenced to profit from the immediate effects of contingency management, followed by the enduring cognitive behavioral therapy (Rawson et al., 2002).

It has been argued that the regulation of intentional behavior varies along a continuum from autonomous (i.e., self-determined) to controlled (Deci et al., 1987). The two paradigms are generally considered as complementary, and both organism and environment are regarded to be important (De Mey, 2003). Analogue to Sabelli's theory of extended thermodynamics, it may be so that the less complex behavioral modality (contingency oriented) must be met first before the more complex cognitive systems can be addressed. (Sabelli & Carlson-Sabelli, 1989). Therefore it may be considered favorable to integrate both frameworks (Marlatt, 2001).

Hence, it might be concluded that cognitive processes mediate stimulus-response relationships (see also George & Marlatt, 1983). Further research on these intrinsic and extrinsic processes, and how these structures interact, is needed.

Finally, some comments can be made pertaining to the operant reinforcement framework of CRA. The need for pharmacological strategies fit well in the behavioral paradigm. Several pharmacological strategies have been outlined and agents such as acamprosate, buprenorphine, disulfiram, methadone and NTX prevent the positive reinforcement of alcohol and illegal drugs. Even innovative

options such as vaccines reduce behavioral effects, by altering the molecular structure and thus limiting the amount of active substances that enters the brain. Moreover, CRA encompasses strategies that are capable of interfering directly with the stimulus-response relationship related to substance use disorders. In addition, CRA employs cognitive-motivational elements needed to initiate and foster sustained abstinence. In this light, CRA may fulfill the call for a multi-modal strategy, which is capable of decreasing the rewarding value of alcohol and drugs and of increasing the uptake of natural rewarding activities, weakening the conditioned-learned drug responses, and advancing the enhancement of cognitive control (Volkow, Fowler & Wang, 2003).

8.4. Recommendations

Based on this thesis some final recommendations can be made to improve the treatment and care for addicted patients:

1. CRA can be regarded as an effective treatment and should be implemented more broadly in normal clinical practice. However, to pursue an accumulation of evidence on the broad spectrum of CRA in substance use disorders, a larger number of studies (RCTs) should be conducted. Other research groups should be involved to conduct these studies. These trials should include a larger number of subjects, in which the sample size is determined by a power analysis. Furthermore, research on CRA should have a follow-up of one year or longer, so that the magnitude of the effect of CRA during a longer term can be established.
2. Pertaining to the conceptual content of CRA, dismantling studies should be conducted to explore the active components. Furthermore, the amount, intensity and mechanisms of these CRA components should be further established by means of an expert group. This will enable us to tailor a CRA treatment, which is protocol driven and gives the opportunity to assess the treatment adherence through tape/video recording. In addition, CRA studies

should be conducted with a broad spectrum of pharmacotherapies with and without contingency management and with multiple follow-up measurements, so that the (auxiliary) value of this program can be evaluated with a higher reliability.

3. To implement CRA in addiction treatment services, far-reaching interventions on normative and cultural aspects should be executed. It is rather optimistic to assume that training will be enough to get these therapists to employ CRA. However, as already suggested, it seems possible to train therapists, especially those without concurrent premises on the terrain of addiction. Another issue concerning implementation is related to the tasks of physicians and CRA therapists. The CRA therapist should integrate the pharmacotherapy in the psychosocial context and monitor adherence to the medication regime. The change in tasks of both the mental health professional and physician makes it indispensable to govern the integral CRA treatment by well-trained health professionals. Bilateral communication between the physician and therapist seems an important issue in this respect.
4. The role of CRA might influence the tasks and treatment strategies of inpatient facilities. CRA is preferably an outpatient treatment, which focuses on reinforcers in the natural context of the subject. This includes social interactions with concerned significant others, recreational and vocational development etc. The role of inpatient facility might compromise the reinforcement premises and therefore should be modified by aiming at pragmatic goals such as the treatment of overdoses and detoxification in patients at high risk for psychiatric and medical complications. However, subjects without a social network or stable housing might benefit from inpatient treatment that aims on (synthetic) network development. This might be also the case for treatments provided in prison. Later on in treatment, CRA can be provided in an outpatient treatment context. These propositions might have drastic effects on the landscape of inpatient and outpatient facilities.

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Summary

Summary

Communitiy Reinforcement Approach and Naltrexone in the Treatment of Addiction

Addiction is a chronic relapsing disorder with medical, legal, psychological and social causes and consequences (see C*hapter one*). Treatment should take all these aspects into account. Therefore, pharmacological interventions should be integrated with psychosocial treatments. Treatment goals vary from cure, through care, to palliation. An important goal of many patients is abstinence.

To facilitate change in addictive behaviors a broad spectrum of psychosocial and pharmacological treatments has been developed. A comprehensive treatment, which integrates psychosocial and pharmacological approaches, is the Community Reinforcement Approach (CRA). Nathan Azrin and George Hunt devised CRA in the early seventies and based it on Skinner's operant learning paradigm. CRA focuses on the replacement with an alternative lifestyle that is more rewarding than a substance using one. CRA attempts to increase natural positive reinforcement from different life-areas such as vocational, recreational and social, by sampling rewarding resources contingent on non-substance related behaviors. Because of this, CRA is regarded as time-consuming and labor intense. CRA interventions such as home visits and social and recreational clubs may illustrate this issue. This may be an important reason that CRA is hardly ever implemented in normal clinical practice.

Although several reviews have outlined the benefit of CRA in terms of the cost-effectiveness, there is lack of evidence of CRA integrated with pharmacological agents such as the opioid antagonist naltrexone (NTX). NTX has been approved for the treatment of opioid and alcohol use disorders in Europe and the USA.

This dissertation focuses on an evaluation of the CRA concept and its effectiveness for the treatment of alcohol, opioid, tobacco and cocaine dependent

patients. Furthermore, the efficacy of NTX, and its combination with CRA are explored. These issues are addressed by means of reviews and empirical studies about the content and effectiveness of CRA, the prescription of NTX, and the combination of both interventions for patients with substance use disorders.

Chapter two deals with the content of CRA. This study examined the concept of CRA by means of the extraction of CRA components out of the available literature. A literature search in electronic databases up to March 2002 was conducted. The analysis ascertained an increase in the CRA components during three consecutive seminal studies. More recent studies varied substantially in number of CRA components. Several new components have been included over time, and have consequently obscured the mechanism of treatment actions. Eighteen components are identified. Dismantling studies are needed to explain the variability of each component in the effectiveness of CRA.

Chapter three examines the effectiveness of CRA by way of a systematic review with meta-analyses. The objectives of this study were to assess the effectiveness of (1) CRA compared with usual care, and (2) CRA versus CRA plus contingency management. Studies were selected through a literature search in electronic databases up to March 2002. Evidence was obtained for the effectiveness of CRA in various substance-related disorders, including alcohol, cocaine and heroin. More studies are needed to substantiate the findings.

Chapter four reviews the effectiveness of NTX and the added value of psychosocial treatment in the maintenance treatment of opioid and alcohol use disorders. The included studies were selected through a literature search, conducted in March 2004. Due to non-compliance, the role of NTX in the maintenance treatment of opioid dependence is unclear. The studies on alcohol dependence showed favorable results regarding the effects of NTX on the medium term, in terms of relapse rate and the percentage of drinking days. The opioid studies combined NTX with a broad variety of psychosocial interventions, which complicated the evaluation of the beneficial effects. Concomitant psychosocial interventions used in the alcohol studies were mainly cognitive behavioral, which may have synergistic action when combined with NTX. Nevertheless, the combination resulted in substantial levels of dropout and non-compliance.

In *Chapter five* data from a pilot study are provided regarding CRA combined with NTX in the treatment of opioid-dependence, by using a pre-post design. Rapid detoxified methadone dependent patients (n = 24) received CRA and NTX maintenance. After six months of treatment, 58% (14/24) of the patients had not relapsed and after one year at least 55% (12/22) still met the initial goal of continuous abstinence.

In *Chapter six* more data are provided about the effectiveness of CRA combined with NTX in detoxified opioid dependent patients. Four outpatient addiction treatment centers in the Netherlands recruited 272 patients from methadone maintenance programs. After rapid detoxification all participants were transferred to CRA and NTX maintenance for a period of ten months. CRA was administered according a protocol encompassing 23 sessions (10 sessions delivered by a psychosocial therapist and 13 sessions delivered by a physician). At 6 months follow-up the cumulative abstinence rate was 24%. It can be concluded that for a relative large subgroup of abstinence-motivated patients, who are participating in a methadone maintenance program, stable abstinence is a feasible goal. As such, the combination of CRA and NTX may comprise a clinically significant alternative for opioid dependent patients.

Chapter seven describes the effects of another pilot study, in which the combination CRA, NTX, and transdermal nicotine patches were explored. Twenty-five smoking recovered spontaneous pneumothorax participants received 8 weeks of treatment. The transdermal nicotine patches were administered for 1 week. The CRA treatment was protocol driven and took 5 sessions. Craving significantly declined between each measurement and there was a significant interaction between decline in craving and the craving measured at baseline. Although not statistically significant, the abstinence rate in the CRA group was higher than in the non-therapy group (46% versus 25%) at three months of follow-up.

Chapter eight involves a discussion on reviews and empirical studies included in this dissertation. The conclusion can be drawn that CRA constitutes an effective treatment to manage a wide range of addictive behaviors. Furthermore, it can be concluded that NTX is an effective agent under the condition that

patients are compliant. The combinations of the various CRA components, including pharmacological options such as NTX, were found to contribute to successful outcome in the treatment of substance use disorders. CRA can be employed to address either abstinence or non-abstinence (moderation) goals to deal with addictive behaviors combined with a broad range of pharmacological agents. Several new strategies are discussed to increase the efficacy of pharmacotherapy, but all call for psychosocial integration. Psychosocial interventions should encompass both behavioral regulation and cognitive-motivational techniques. Both aspects may be sequenced to benefit from the immediate effects of behavioral reinforcement principles, followed by enduring cognitive motivational therapy. More research is needed on how these structures interact.

Finally, CRA is a powerful multi-modal strategy. It outweighs the rewarding value of alcohol and drugs and increases the exposure and uptake of natural rewarding activities. Therefore CRA should be implemented in normal clinical practice.

Samenvatting

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Communitiy Reinforcement Approach en Naltrexon in de Behandeling van Verslaving

Verslaving is een chronisch recidiverende stoornis met medische, justitiële, psychologische en sociale oorzaken en consequenties (zie *hoofdstuk 1*). Om positieve behandelresultaten te bevorderen dient bij behandeling met al deze aspecten rekening te worden gehouden. Om deze redenen dienen farmacologische interventies geïntegreerd te worden met psychosociale behandelingen. De behandeldoelen variëren van abstinentie, naar stabilisatie van het gebruik, tot palliatieve zorg. Een belangrijk doel voor veel patiënten is abstinentie.

Verschillende psychosociale alsmede farmacologische behandelingen zijn ontwikkeld met als doel verandering te bewerkstelligen in verslavingsgedrag. Een behandeling die de psychosociale en farmacologische benadering integreert is de Community Reinforcement Approach (CRA). Nathan Azrin en George Hunt ontwikkelden CRA begin jaren '70 en baseerden het op de operante leertheorie van Skinner. Middelengebruik wordt in deze context beschouwd als gedrag dat onder invloed staat van operante bekrachtiging, waarbij de relatie tussen gedrag en uitkomst relevant is. CRA benadrukt dat afhankelijkheid van middelen in stand wordt gehouden door drugsgerelateerde bekrachtigers en door een gebrek aan alternatieve niet verslavingsgebonden bekrachtigers. Daarom richt CRA zich op het ontwikkelen van een nieuwe leefstijl die meer belonend is dan middelengebruik, door te interveniëren op bekrachtigers in de directe omgeving van de verslaafde, zoals in het gezin, het werk, woonomgeving, vrienden, tijdsbesteding en dergelijke. Om deze reden wordt CRA gezien als een tijdsconsumerende, intensieve behandelvorm. CRA interventies, zoals huisbezoeken en de ontwikkeling van sociale en recreatieve clubs of

gezelschappen, illustreren deze kwestie. Het is wellicht een belangrijke reden waarom CRA slechts beperkt wordt toegepast in de klinische praktijk.

Hoewel een aantal reviews laat zien dat CRA een kosteneffectieve behandeling is, is er gebrek aan bewijs voor CRA geïntegreerd met farmacologische interventies, zoals de opiaatantagonist naltrexon (NTX). NTX is geregistreerd voor de behandeling van heroïne en alcoholverslaving in Europa en de VS.

Deze dissertatie richt zich op de evaluatie van het CRA concept en de effectiviteit in de behandeling van middelen gebonden stoornissen. Verder wordt de effectiviteit van de combinatie CRA en NTX onderzocht door middel van systematische reviews en empirische studies. Deze gaan over de inhoud en de effectiviteit van afzonderlijk CRA en NTX, en de combinatie van beide interventies voor patiënten met een heroïne verslaving.

Hoofdstuk 2 heeft betrekking op de inhoud van CRA. In deze studie is het concept CRA onderzocht door middel van een zoekstrategie, waarbij elektronische databestanden tot maart 2002 werden geraadpleegd. De resultaten gaven een toename aan in het aantal CRA componenten in de eerste drie opeenvolgende studies. Meer recente studies variëren in het aantal gebruikte CRA componenten. Verschillende nieuwe componenten zijn in de loop der tijd toegevoegd. De samenvoeging van deze componenten zorgde ervoor dat het niet duidelijk is welke componenten een actieve rol spelen. Achttien verschillende componenten zijn geïdentificeerd. Ontmantelende studies zijn nodig om de effectiviteit van elke individuele component te verklaren ten opzichte van de totale effectiviteit van CRA.

Hoofdstuk 3 onderzoekt de effectiviteit van CRA middels een systematische review met behulp van meta-analyses. De doelstelling van deze studie was het vaststellen van de effectiviteit van: (1) CRA vergeleken met de gewone zorg, en (2) CRA versus CRA met 'contingency management' (d.m.v. vouchers). Studies werden geselecteerd op basis van een literatuurstudie in elektronische databestanden tot maart 2002. Over het algemeen is er bewijs voor de effectiviteit van CRA bij diverse middel gebonden stoornissen. Er zijn meer studies nodig om de bevindingen te bevestigen en te kunnen generaliseren.

Hoofdstuk 4 gaat in op de effectiviteit van NTX en de toegevoegde waarde van psychosociale behandeling in de onderhoudsbehandeling van heroïne- en alcoholverslaving.
De studies zijn geselecteerd door een literatuurstudie, uitgevoerd in maart 2004.Ten gevolge van beperkte therapietrouw blijft de rol van NTX in de onderhoudsbehandeling van opiaatverslaving onduidelijk. De alcoholstudies laten zien dat NTX effectiever is dan een placebo in termen van terugvalpercentage en het percentage drinkdagen op de middellange termijn. De opiaatstudies combineerden NTX met een breed scala aan psychosociale interventies, hetgeen de evaluatie van de meerwaarde compliceerde. De psychosociale interventies die gebruikt werden in de alcoholstudies waren hoofdzakelijk cognitief gedragsmatig van aard. De combinatie heeft wellicht een gunstig effect op het voorkomen van terugval. Echter, de psychosociale interventies hebben onvoldoende invloed op het voorkomen van uitval en gebrek aan therapietrouw.

In *hoofdstuk 5* worden er gegevens gepresenteerd vanuit een pilotstudie, waarin heroïneverslaafden een gecombineerde behandeling van CRA met NTX kregen aangeboden. Er werd gebruik gemaakt van een pre- en postmeting. Vierentwintig methadonafhankelijke patiënten ontvingen, na snelle detoxificatie, CRA en een onderhoudsdosering NTX. Na zes maanden behandeling bleef 58% (14/24) abstinent, na een jaar haalde ten minste 55% (12/22) het vooraf gestelde doel van continue abstinentie. De combinatie CRA en NTX, in de vorm van een intensieve ambulante begeleiding, lijkt daarmee een veelbelovende benadering.

In *hoofdstuk 6* worden er meer gegevens gepresenteerd met betrekking tot de effectiviteit van de combinatie CRA en NTX behandeling bij gedetoxificeerde heroïneverslaafden. Vier ambulante behandelcentra in Nederland rekruteerden 272 patiënten vanuit methadonprogramma's. Na een snelle detoxificatie kregen de deelnemers, voor de periode van tien maanden, de gecombineerde behandeling van CRA met NTX onderhoudsdosering aangeboden. De behandeling was geprotocolleerd en omvatte 10 sessies bij de CRA therapeut en 13 sessies bij de CRA arts. Op maand zestien is 32% van de patiënten abstinent en is 24% van de patiënten gedurende de gehele follow-up van 16-maanden voortdurend schoon gebleven (continue abstinentie), zonder een periode van

terugval. Voorts zijn er verschillen in termen van gezondheidswinst tussen de deelnemers die abstinent bleven ten opzichte van de deelnemers die terugvielen in heroïnegebruik. Deze gezondheidswinst geldt o.a. voor het gebruik van psychotrope stoffen, psychische klachten ernst van verslaving (ASI), craving en kwaliteit van leven. Voor een relatief grote subgroep methadonpatiënten, die gemotiveerd zijn voor abstinentie, is stabiele abstinentie een haalbaar doel. Hoewel het design het niet toelaat om de effecten volledig toe te schrijven aan de CRA en NTX behandeling, zijn de uitkomsten op zijn minst bemoedigend te noemen en lijkt de combinatie van CRA met NTX een klinisch significant alternatief voor patiënten met een heroïneverslaving.

Hoofdstuk 7 geeft een beschrijving van een andere pilotstudie waarbij de combinatie CRA en NTX en nicotinepleisters werd onderzocht bij de behandeling van rookverslaving. Vijfentwintig deelnemers die hersteld waren van een spontane klaplong (Spontaneous Pneumothorax) kregen acht weken een combinatie behandeling. Nicotine pleisters werden voor de duur van één week aangeboden en langzaam afgebouwd. NTX werd verstrekt gedurende de gehele behandeling. Het CRA programma bestond uit 5 geprotocolleerd sessies. De craving verminderde voor de gehele groep statistisch significant over de tijd. Meer patiënten in de CRA conditie waren abstinent in vergelijking tot de non-therapie groep, na 3 maanden follow-up (46% versus 25%). Echter deze bevinding was niet statistisch significant. Desalniettemin lijkt CRA een interessante interventie voor deze doelgroep.

Hoofdstuk 8 bevat een discussie over de reviews en empirische studies die gedaan zijn in deze dissertatie. De bevindingen laten zien dat CRA effectief is in de behandeling van verschillende middelen gebonden stoornissen. Er kan worden verondersteld dat NTX alleen een effectief middel is als voldaan wordt aan therapietrouw. De combinaties van de verschillende CRA componenten, waartoe ook farmacologische opties zoals NTX gerekend kunnen worden, dragen bij tot een succesvolle uitkomst in de behandeling van verslaving. Welke componenten precies effectief of overbodig zijn blijft onduidelijk. Studies gericht op een verdere ontleding van deze kwestie zijn nodig om meer helderheid te kunnen verschaffen over de specifiek werkzame CRA-componenten.

De CRA behandeling kan worden toegepast voor zowel abstinentie- als niet abstinentiedoelen (moderatie van het gebruik) en kan worden gecombineerd met een breed aanbod aan farmacologische middelen. Diverse nieuwe strategieën worden bediscussieerd om het effect van farmacotherapie te vergroten, maar alle strategieën dienen geïntegreerd te worden in een psychosociale behandelvorm. Psychosociale interventies zouden zowel gedragsregulatie als cognitief-motivationele technieken moeten bevatten. Er lijkt bestaansrecht voor de stelling dat beide aspecten opeenvolgend zouden moeten plaatsvinden voor optimaal effect. Echter, meer onderzoek naar de interactie tussen deze structuren is nodig.
Ten slotte, CRA is een multi-modale strategie om de blootstelling aan positieve bekrachtigers te vergroten, zodat het repertoire van natuurlijk beloningsgedrag wordt uitgebreid, om de belonende waarde van alcohol en drugs te reduceren. Gezien de effectiviteit kan implementatie in de klinische praktijk worden aanbevolen.

Dankwoord (Acknowledgements)

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Deze dissertatie was er niet geweest zonder de inbreng van veel mensen. Een aantal mensen wil ik daarom noemen voor hun bijdrage aan deze dissertatie.

Speciale aandacht wil ik laten uitgaan naar de promotoren en copromotoren die mij hebben geïnspireerd, gesteund, en veel tijd hebben besteed aan het nazien en becommentariëren van dit werk. Als eerste wil ik Cor de Jong bedanken voor de mogelijkheid die hij mij heeft gegeven om te kunnen promoveren. Je hebt mij in de gelegenheid gesteld om kennis te maken met verschillende facetten die komen kijken bij onderzoek in een multi-center verband (EDOCRA). Je voortvarendheid en je pragmatische aanpak, gekoppeld aan een enorme drijfveer om wetenschappelijk onderzoek en praktijk met elkaar te verbinden, zijn voor mij een bron van inspiratie geweest. Je brede kennis op het terrein van verslavingszorg en psychiatrie zijn voor mij zeer waardevol geweest. Daarnaast heb ik genoten van je culinaire hoogstandjes en de vele etentjes. Gerard Schippers wil ik in het bijzonder bedanken voor zijn wetenschappelijke inbreng in de totstandkoming van deze disseratie. Ik heb genoten van jouw rijke kennis en visie op het gebied van therapieën om verslavingsgedrag aan te pakken. De wijze waarop je trainingen verzorgt en je kennis overdraagt is ongeëvenaard. Maar ook je geduld en het vermogen om een heldere lijn aan te brengen als ik het spoor bijster was, zorgen ervoor dat ik terugkijk op een plezierige samenwerking. Verder wil ik Wim van de Brink bedanken voor de samenwerking, die inmiddels al ruim 10 jaar duurt. Na mijn afstuderen ben jij voortdurend betrokken geweest bij vrijwel al mijn wetenschappelijke ondernemingen. Ik ben nog steeds diep onder de indruk van je wetenschappelijke kwaliteiten en enorme snelheid en efficiëntie die je bezit. Ik ben dan ook verheugd dat ik altijd aanspraak kon maken op je tijd om mij te helpen in het verhogen van de kwaliteit. Ook wil ik Ad Kerkhof bedanken. Jou ben ik al tegengekomen in Leiden bij mijn stage en scriptie. Het is een voorrecht om zo'n begeleider te hebben die mij al zo lang bijstaat in het doen van wetenschappelijk onderzoek. Onvermoeibaar heb je menig tekst die ik aanleverde gecorrigeerd, en telkens wanneer ik dreigde vast te lopen, wist je me toch weer te motiveren om de draad

weer op te pakken. Je brede kennis op het gebied van psychotherapieën, suïcide preventie en depressie hebben mij geboeid. Daarnaast heb je mij altijd de ruimte en het vertrouwen gegeven zodat ik mij kon ontplooien. Voorts heb ik onze vele persoonlijke ontmoetingen als zeer plezierig mogen ervaren.

Verder wil de promotiecommissie bedanken voor het lezen en beoordelen van deze dissertatie: Prof. Dr. H.M. van der Ploeg, Prof. Dr. J.M. Koot, Prof. Dr. M. van Son, Prof. Dr. P. Postmus, Dr. V.H. Hendriks, en Dr. M.H.M. Breteler. Rien Breteler en Piet Postmus wil ik graag nog in het bijzonder bedanken voor de samenwerking met de rookstudie, en Rien bedankt dat je de moeite hebt genomen om mij nog een aantal opmerkingen en aanwijzingen te sturen. Henk van der Ploeg wil ik bedanken voor de hulp in de eindfase van mijn werkzaamheden aan de VU.

Veel dank ben ik verschuldigd aan de collega's van het Ambulante Team Westelijk en Noord-Brabant te Roosendaal. Dit is vanaf medio jaren '90 mijn vaste werkplek geweest, waar ik mij mede dankzij jullie inzet me heb kunnen ontwikkelen op klinisch en onderzoeksgebied. De oud collega's Jeff, Jan Pieter, Ad Jan, Ton, Tom, Noa en Mirjam wil ik bedanken voor hun aandeel en de vele leuke momenten die ik met hen heb beleefd. Ook het Ambulante Team van Breda wil ik bedanken voor hun ondersteuning en begrip. Romko de Kan wil ik bedanken voor de medische ondersteuning in de pilotstudie. Peter Geerlings wil ik bedanken omdat hij mij het duwtje heeft gegeven om aan deze promotie te gaan beginnen.

Ook wil ik de medewerkers van afdeling Klinische Psychologie van de VU bedanken voor al hun inspanningen en medewerking die zij hebben verleend aan het onderzoek. Evenzo wil ik alle studenten bedanken die hebben meegewerkt aan de rookstudie. Verder wil ik alle medeauteurs bedanken voor hun bijdrage aan de manuscripten. In het bijzonder wil Peter Dekker bedanken voor de hulp bij de statistische analyses, bij wie ik altijd terecht kon. Ranne wil ik nog speciaal bedanken voor de samenwerking op de VU en nadien bij Kentron. Het is leuk om met jou reviews te doen na werktijd.

Verder wil ik alle collega's bedanken die betrokken zijn geweest bij EDOCRA. Het zijn er teveel om op te noemen maar ik wil Gemma van der Wouw, Riëtte van Westen, Thinka van der Heiden, Renate Elfrink, Cor Verbrugge, Jannette Bolck,

en Jessica Schippers specifiek noemen. Ook de mensen van de verschillende detox afdelingen, CRA artsen en therapeuten wil ik bedanken voor de goede zorg van de EDOCRA cliënten. In het bijzonder wil ik Annette Ruijsink, Petra van de Kroft en Kathinka Damen bedanken voor de leuke tijd en de gezelligheid. Ook wil ik Evelien, Boukje, en Marloes succes toe wensen met de afronding van hun proefschrift. Laura wil bedanken voor haar opbeurende gesprekken en ik wil haar sterkte wensen met haar CRA & vouchers studie.

Onno van Logchem wil ik bedanken voor zijn aandeel in de lay-out. Zonder jou had dit boekje er echt niet op tijd gelegen. Je hebt de nodige vrije uurtjes opgeofferd om mij te helpen. Ook wil ik Onno van Beek bedanken bij de hulp en creativiteit bij de totstandkoming van het kaft. Aad Dijksman wil ik bedanken voor de vele adviezen en steun die hij mij heeft gegeven tussen het gitaarspelen door.

Voorts de paranimfen. Eric vanaf het moment dat ik je tegenkwam op de VU klikte het tussen ons. Ik kijk dan ook terug op een zeer plezierige tijd met je waarin we behoorlijk wat lief en leed hebben gedeeld. Daarnaast kon ik altijd bij je terecht om gebruik te kunnen maken van onderzoekskwaliteiten en je vermogen om mijn werk kritisch te beoordelen. Eric heel erg bedankt. Reinoud, dank dat je nog op de valreep stukken wilde nazien, zo midden in de situatie dat je net opnieuw vader bent worden. Dat laatste geldt ook voor Marco. M.G.J. fantastisch dat je mijn 'reserve' paranimf wilde zijn. Jullie zijn altijd geweldige vrienden voor mij geweest en koester de bijzondere momenten die wij in de loop van de tijd hebben beleefd.

Tevens wil ik mijn familie, en in het bijzonder mijn moeder bedanken. Hoewel het onderwerp misschien niet altijd duidelijk voor je was, heb je wel altijd geïnformeerd met betrekking tot de vorderingen. Dank hiervoor. Tenslotte wil ik mijn partner Mascha bedanken voor haar liefde, steun en toewijding om mij door de diverse moeilijke fasen van het onderzoeksproces heen te loodsen. Ik heb daarmee echt mazzel. Ik ben je veel dank verschuldigd voor al je tijd en hulp.
Ik weet zeker dat ik nog veel mensen ben vergeten. Deze wil ik hierbij alsnog bedanken.

About this Dissertation

About this dissertation

In the spring of 1995 a new treatment became available for Dutch opioid addicts: Naltrexone (NTX) assisted rapid detoxification under full anesthesia (Legarda & Gossop, 1994). The treatment was offered by a commercial organization in Spain: Centro de Investigatión y Tratamiento de la Addición (CITA). This approach (Ultra Rapid Opioid Detoxification (UROD®)) attracted many drug users, since it claimed that UROD was painless and much faster (within 24 hours) than regular detoxification programs, which usually take weeks to complete. Following detoxification, patients were encouraged to continue with oral NTX as a maintenance treatment to prevent relapse. CITA claimed that about 70% of the eligible clients were abstinent for 6 months or longer.

Some Dutch opioid dependent patients flew to Spain to enroll in this new treatment. The first patients were referred from a methadone maintenance program in Roosendaal to the CITA treatment center in Sevilla. Following discharge, several patients with a long history of opioid abuse remained abstinent for several months. The first impression was that the observed results were much better than those of regular clinical methadone tapering programs followed by usual relapse prevention programs.

Encouraged by these results, I decided to go to Madrid to meet Dr. Juan Jose Legarda, founder of CITA, to obtain information about this experimental procedure. In this meeting in autumn 1995, Dr. Legarda provided detailed information about the UROD procedure. It was allowed to observe a rapid detoxification procedure with two patients from Greece.

The new medical procedure was interesting, but what really drew attention were the elaborate family involvement and the friendly and professional attitude of the staff. Dr. Legarda acknowledged the mandatory need for appropriate aftercare to prevent relapse. In his perspective, available family resources were to be sampled to foster abstinence, by monitoring and guarding compliance of treatment attendance and the medication (NTX) regime. Furthermore, the family

was involved in the treatment program to explore reinforcers contingent on abstinence. Finally, patients were not treated as addicts, but as patients situated in a general hospital.

The key components of this method seemed to be (1) the innovative medical approach, to quickly detoxify subjects from opioids and induce a NTX maintenance program, (2) the integral treatment using a network approach, and (3) selection of subjects motivated to be charged by approximately Euro 5,000.

This introduction into the UROD methodology suggested that the claimed successes of the treatment were primarily based on the biological ingredients. However, the active psychosocial components, such as the embedding of the treatment in the traditional South-European family structure and addressing in many respects positive reinforcement, seemed also to contribute to the positive treatment outcomes.

In observing the program, there was a resemblance with components of the Community Reinforcement Approach (CRA) as it was developed and practiced in the US by Hunt and Azrin (e.g. Azrin et al., 1982).

CRA integrates pharmacological agents and/or medical procedures, family support and psychological interventions. A positive reinforcement approach seems to constitute a key concept in the successful treatment. However, literature reviews indicated that CRA had not been extensively studied (e.g. Finney & Monahan, 1996). Despite its resemblance, the Spanish authors did not mention CRA as source for the psychosocial component of their success story. In fact, no studies were available on CRA combined with rapid opioid detoxification (ROD), with or without anaesthesia, let alone on CRA integrated with NTX as a relapse prevention treatment.

Therefore, in February 1996, we started a program to detoxify methadone maintenance patients with a rapid NTX assisted detoxification procedure without anaesthesia, embedded in a CRA-based psychosocial program. The initial results of this pilot were encouraging (Roozen et al., 1997). Subsequently, we

participated in a randomized multi-center study with the acronym EDOCRA[2], in which two types of NTX assisted rapid opioid detoxification (with and without anesthesia) were followed by NTX maintenance treatment combined with a CRA-based treatment (De Jong et al., 2004). These experiences with CRA and NTX assisted rapid detoxification form the underpinning of this dissertation.

In Europe research on ways to bolster the therapeutic efficacy of CRA is negligible. This dissertation scientifically evaluates the concept and the effectiveness of CRA (and NTX) in the treatment of patients with substance use disorders.

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Curriculum Vitae

Curriculum Vitae

Hendrik Gerrit Roozen werd geboren op 6 januari 1968 te Doetinchem. Hij bezocht in Doetinchem het Ulenhof College. Daar startte hij in 1980 op de MAVO om met een HAVO en VWO-diploma in 1989 Gelderland te verlaten voor verdere studie.

In Delft ging hij Mijnbouwkunde en Petroleumwinning aan de Technische Universiteit studeren. Hij werd daarnaast lid van het Delftsch Studentencorps. Hij behaalde zijn Propedeuse in 1991 en besloot vervolgens psychologie te studeren aan de faculteit der Sociale Wetenschappen aan de Universiteit Leiden.

Van 1991 tot 1996 studeerde hij aan de faculteit Klinische en Gezondheids-psychologie en in zijn afstudeerproject onderzocht hij de toepassingen van CRA en naltrexon bij opiaatverslaafden in de (ambulante) Nederlandse verslavings-zorg. Deze scriptie werd genomineerd voor de scriptieprijs.

Hij bleef na zijn stage en onderzoek bij Novadic-Kentron werken. In 1996 haalde hij zijn basisaantekening NIP en in de periode 1998 tot 2004 volgde hij cursussen voor zijn registratie van Gezondheidszorgpsycholoog. Deze registratie werd in 2004 een feit.

Hij is momenteel werkzaam bij Novadic-Kentron als psycholoog en is hoofdbehandelaar van de ambulante teams in Roosendaal en Breda.

In 1999 werd hij promovendus, verbonden aan de Vrije Universiteit te Amsterdam. Zijn promotieonderwerp is "Community Reinforcement Approach and Naltrexone in the Treatment of Addiction". De onderzoeksschool betrof het Research Institute Psychology & Health te Utrecht.

In de publicatielijst kunt u zijn artikelen en presentaties vinden. Naast onderzoek heeft hij als gast reviewer diverse artikelen gereviewd voor o.a. Addiction, Archives of General Psychiatry, Cochrane Drug and Alcohol Group, en Drug and Alcohol Dependence.

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